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STIG WIKSTRÖM

**Propulsive gastrointestinal
motility in regional
and graded ischemia of
the small bowel**

An experimental study in the rat

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University of Uppsala, Sweden*

Propulsive gastrointestinal
motility in regional
and graded ischemia of
the small bowel

An experimental study in the rat

I. Immediate results

by GUNNAR NYLANDER
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STOCKHOLM 1968



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Introduction

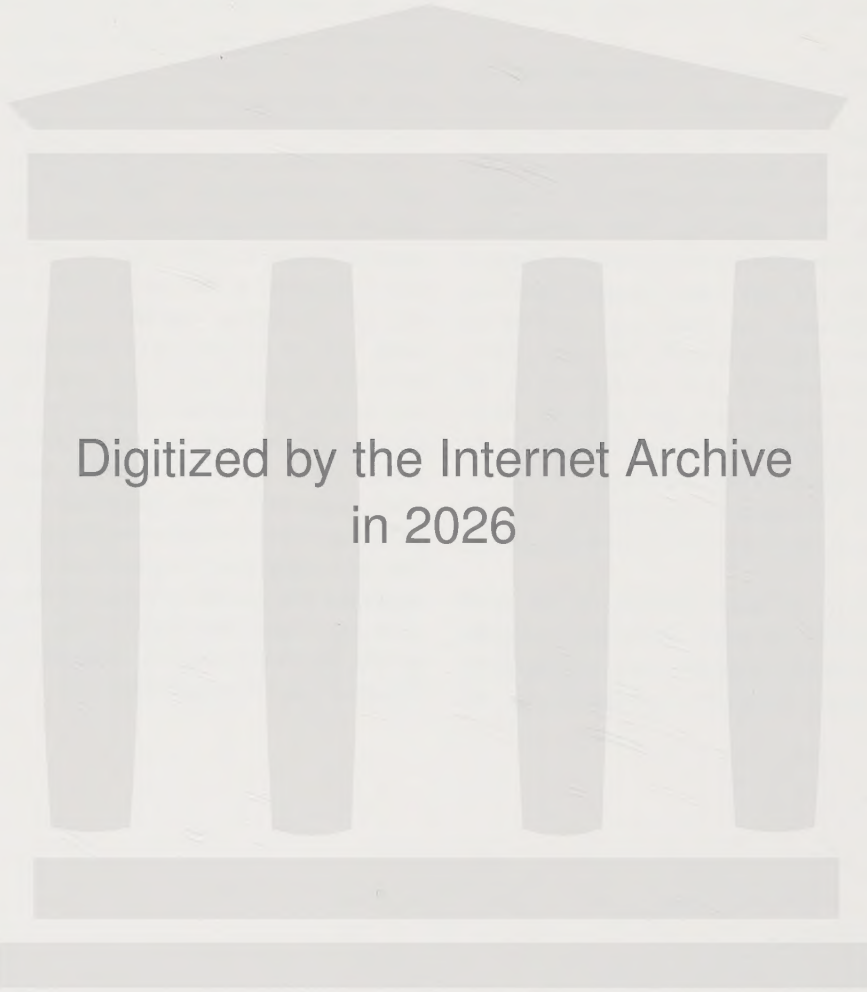
There are many indications that obliterative arteriosclerosis is an increasingly common cause of symptoms from different organs. In this respect the gastrointestinal tract is no exception despite the considerable capacity of the large splanchnic vascular bed.

It is primarily the total and acute interruption of circulation in the superior mesenteric artery and vein which dominates our conception of vascular disease in the small bowel. A number of experimental and clinical observations, however, form grounds for assuming that obliterative changes in the mesenteric or intramural vessels of the intestine are not only more common than was previously supposed, but also cause abdominal symptoms. Very little is known, however, about the actual occurrence of such restrictions in the intestinal blood supply, and the extent to which they can be wholly or partly compensated for by collateral circulation. Our knowledge of the effect of such circulatory disturbances on the morphology and functions of the intestine is also deficient.

When a large or small fraction of the small bowel is affected by such obliterative vascular changes, it is highly probable that, among other things, its motor function is damaged, at any

rate in the immediate phase. Possibly, the neuromuscular structures of the intestinal wall, which initiate and maintain the propulsive motility of the intestine, are affected in different ways, so that the tissue changes which occur either excite or paralyze this motor system. Whether the effect is excitatory or paralytic may depend on the degree of severity and the extent of the regional ischemia.

Conditions of this kind have never been elucidated experimentally. They are not, however, without clinical significance, since disturbances in gastrointestinal motility can greatly influence the other functions of the small intestine, and especially its absorption capacity. The effect on the latter can be all the more deleterious, since the ischemic damage *per se* can more or less reduce the normal absorption capacity of the intestine. Many such transient or enduring disturbances in small bowel motility, secretion and absorption, often associated with abdominal discomfort and pain, may have a vascular background. It is therefore an urgent task to ascertain how a regionally restricted and varied ischemia in the small bowel influences these functions. In this work the effect on the propulsive motility function of the gastrointestinal tract is mainly analyzed.



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Chapter I. Review of the Literature

VASCULAR SUPPLY TO THE SMALL INTESTINE

Mesenteric Vessels

In order to understand the result of reduced blood flow to the small bowel it is important to know the functional anatomy of its vascular area.

The description of the arteries is, in each individual case, applicable to the corresponding veins.

The superior mesenteric artery supplies that part of the gastrointestinal tract which has developed from the embryonic midgut, i.e. large parts of the duodenum, the rest of the small bowel, and the large bowel up to the middle of the transverse colon. This artery has only insignificant anastomoses with adjacent vascular areas. Both the pancreatico-duodenal arteries establish connections with the coeliac artery, and the middle and the left colic arteries with the inferior mesenteric artery.

The superior mesenteric artery ramifies between the two mesenteric folds. In a comparative anatomic analysis, Noer & Manning (1941) stated that, in principle, the ramification pattern is the same in different animal species, even though it may vary substantially in detail. Its vascularity is impressive, with numerous anastomoses both mesenteric and in the intestinal wall; and its anatomic arrangement is such, that the effect of vascular obstruction is largely counteracted.

Most of the detailed descriptions of the topography of the mesenteric vessels are of less recent date. Such vasculo-anatomical studies on human beings have been carried out by Dwight (1903), Monks (1905, 1909, 1929), and Eisberg (1924); on dogs by Eisberg (1925), Bradley (1927), and Dieulafe (1936); on rabbits by Dieulafe (1936); and on rats especially by Weyrauch & De Garis (1937).

The immediate branches from the superior mesenteric artery are called the *intestinal arteries*. Their number varies in different animal species, and this applies also to the part of the small intestine supplied by each of these arteries. During

their course to the mesenteric attachment of the gut the intestinal arteries ramify. Consecutive branches anastomose reciprocally to form so-called *primary arches*, the convexity of which is directed towards the intestine. These give rise to *secondary arches*, which, in turn, form *tertiary arches* etc. In human beings there are five such sequences between the main artery and the mesenteric attachment of the gut. Finally, the arches give rise to arteries, running parallel to one another and reaching one side or the other of the intestine, where they split up. These *straight arteries* supply the intramural, vascular system of the intestine. In the human mesentery they have the appearance of end-arteries though they are not truly so, because of the abundance of mural and antemesenteric anastomoses (Eisberg, 1924). The dog, on the other hand, has a network of vessels along the mesenteric attachment of the gut, which proceeds from the adjoining large arches. Thus, in this case, the straight arteries do not have the appearance of end-arteries, but form a mesenteric border anastomosis, which makes the protection against interruption of circulation still more effective.

The straight arteries supply blood both to the serosa and to deeper layers of the intestinal wall via mural trunks which pierce the muscularis. The direction of the perforating vessels is said to be decisive for the effect that pronounced distention can exert on the blood flow in the intestinal wall (Eisberg, 1924; Dragstedt & Dragstedt, 1922; and Dragstedt *et al.*, 1929).

Mural Vessels

The large vascular plexus in the submucosa supplies the mucosa and the smooth-muscle layers of the intestine. The former, in consequence of its dominant function, has a very ample blood supply. Every villus has a central artery which, without ramifications, reaches its apex. There it divides into two symmetrical, arcade arterioles which run immediately below the epithelial layer. These give off the capillary loops that fill up the

villus, and establish close contact with its epithelium. The capillaries are drained by two veins which are located symmetrically at the base of the villus. They, in turn, communicate with the corresponding drainage from the adjacent villi in the anastomosing venous plexus of the submucosa.

According to Nylander & Olerud (1961) there is the possibility of arteriovenous shunting occurring in a villus when the capillary area is closed off, and blood from the central artery passes, via the arcade arterioles, directly into the basally situated veins. The presence of arteriovenous shunts in the submucosa of the small intestine had previously been suggested by Barlow (1952).

INTESTINAL BLOOD FLOW IN NORMAL CONDITIONS

The vascular bed of the small intestine plays quite a significant role in the physiology of the peripheral circulation. It forms part of the splanchnic vascular bed, which, under normal conditions, receives about 20% of the cardiac output, and at every moment it contains about 25% of the total blood volume (Bashour & McClelland, 1967). The small intestine has a high energy consumption and makes great demands on arterial circulation. Moreover, the portal vein and its roots, together with the liver, function as a substantial blood reservoir whose outflow is controlled by special sphincteric structures in the hepatic veins. Consequently, the circulatory conditions in the splanchnic area are of great importance for the maintenance of the homeostasis of the peripheral circulation.

The mucosa is the essential functional unit of the small intestine. Its vascular bed satisfies the considerable metabolic requirements of the glandular activities and of absorption. Exchange occurs over the thin capillary walls; and, in accordance with their function, these vessels are called *exchange vessels*. The adjacent parts have been given a special nomenclature, which indicates the important regulative functions on both sides of the exchange area (Folkow, 1960, 1967). They are clearly-defined functional units that exert resistance to flow, and are therefore called resistance sections. Of these, the *precapillary resistance section* has the greatest effect on the total

peripheral resistance, and mainly determines the size of the microcirculation. Inflow to the capillary area is regulated by a *precapillary sphincter section* which from time to time determines the number of open capillaries, and hence also such essential factors as size of available exchange area, diffusion distance etc. On the other side of the capillary area is the *postcapillary resistance section* which mainly influences the relation between precapillary and postcapillary resistance. Slight variations in this flow resistance regulate capillary pressure and fluid distribution between capillary blood and tissue. The remaining portion of the venous system of the gastrointestinal tract has the role of a substantial blood reservoir and is consequently called, as a whole, the *capacitance section*. It is able to vary considerably its dimensions and volume of blood, without affecting the total peripheral resistance.

By means of these regulative vascular sections the small intestine can regulate its circulation within very wide limits and vary the size of its capillary exchange surface, the potential capacity of which is enormous (Folkow *et al.*, 1963). In accordance with their special anatomical and functional characters, the mucosa and submucosa receive the larger part of the blood flow, and the smooth muscle layers get about one third of the flow (Grim & Lindseth, 1958; Rayner *et al.*, 1960, Lundgren & Kampp, 1966; Kampp & Lundgren, 1966 *a* and *b*).

Autoregulatory Adjustments

When the arterial blood pressure and flow are reduced for some reason, the myogenic tonus of the precapillary vascular section is immediately lowered (Folkow, 1949; Johnson, 1960). This autoregulation has been subsequently analyzed by Hanson & Johnson (1962), and Johnson & Hanson (1962), who also demonstrated an increase in venous resistance. These mechanisms cooperate to protect the capillary area from disastrous ischemia. The former is a myogenic reflex and the latter a local, sympathetic axon reflex with receptors on the arterial side and effectors on the venous side. Such autoregulation is produced, according to Bean & Sidky (1957) also by tissue anoxia irrespective of its origin.

In order to protect the capillary area from the effect of increased venous pressure, transmission is compensated for, according to Johnson (1965)

by precapillary constriction and postcapillary dilatation; the latter is the dominant factor.

Another autoregulative mechanism has been described by Folkow *et al.* (1964 *a* and *b*). The effect of continued sympathetic outflow ceases after a time owing to an "autoregulative escape of the resistance vessels from the constrictor fiber influence". The mucosal blood flow remains reduced but an increase in flow occurs in the submucosa. Such a redistribution of flow shows, according to Folkow (1967) that neurogenic influence can hardly cause any lasting changes in intestinal capillary pressure. This is of essential importance in view of the enormous capillary area of the organ.

Effects of Intestinal Muscle Activity

The effect of rhythmic and tonic contractions on the blood flow in the intestinal wall and the capacity of its veins as a blood reservoir have been analyzed by Sidky & Bean (1958). The *rhythmic* muscular contraction causes a reduction in arterial flow and a pronounced increase in venous outflow. This results in a positive pump effect, which can build up the venous pressure to exceed the arterial pressure, and contribute towards active propulsion of venous blood through the intestinal and hepatic veins. This haemodynamic effect is directly proportional to the strength of the contractions. The arterial inflow increases during the relaxation phase, at the same time as the venous outflow diminishes.

Tonic contraction decreases the flow and can, if prolonged and pronounced, entirely eliminate the effect of the rhythmic contractions.

Thus, smooth muscle activity is of great importance for peripheral flow resistance and functional blood reserve in the small intestine. The effect can be so pronounced that it is superimposed on others, which are thereby strengthened, masked, or even converted into their opposites. The special anatomical structure of the intestinal veins is decisive for this special hemodynamics. Thus, the coarse perforating trunks, that drain the submucosal venous plexus into the mesenteric veins, have valves capable of withstanding comparatively high pressures. Hence the blood cannot return from the venous side. Moreover, the veins have considerable distensibility, with the possibility of storing large blood depots when the intestinal muscle has a low tonus.

Effects of Ingestion of Food

It has long been known that cardiac output increases after meals (Grollman, 1929; Paine & Shock, 1950; Berman *et al.*, 1950). During periods of increased function, the splanchnic organs were long considered to receive increased amounts of blood in relation to that of the other organs of the body (Brandt *et al.*, 1955). It has been convincingly shown, however, that the increase in cardiac output is not only benefited by the splanchnic area, but is supplied equally to all the organs of the body (Herrick *et al.*, 1934; Abramson & Fierst, 1941; Reininger & Sapirstein, 1957).

Certain observations indicate, however, that food releases an autoregulative reflex in the intestine. The peripheral flow resistance is diminished, with increased arterial flow to fulfil the demands of the greater oxygen consumption in the intestinal section concerned (Varró *et al.*, 1967 *a* and *b*).

A moderate decrease in arterial flow does not cause a corresponding reduction in the energy-consuming absorption. Better utilization of the oxygen content of the arterial blood compensates for the reduced flow and explains the discrepancy between these functions (Varró *et al.*, 1965, 1967 *a* and *b*).

IMPAIRED INTESTINAL BLOOD FLOW

As is evident from the foregoing, the small intestine has an especially rich vascularity, the structure of which affords a high degree of security against disturbances of both the arterial and the venous flow. Moreover, the vascular bed of the mucosa is capable of such autoregulation as can ensure, within certain limits, protection for the capillary area against changes in pressure and flow.

Consequently, for an interruption in circulation to prove disastrous it must be located *centrally* or affect a large number of *peripheral* vessels.

Central Vascular Occlusion

This can affect both the *superior mesenteric artery* and *vein*. In the former case the occlusion may be partial with a long period of development, or total and sudden. The cause of arterial occlusion is obliterative arteriosclerosis with or without thrombosis, or embolic material that occludes a normally wide or constricted main artery. The

obliterative thrombosis in the superior mesenteric vein is the result of hypertension or septic infection in the portal area. In rare cases it occurs without any apparent cause.

Partial occlusion

This can permit a blood flow that is sufficient for metabolism at rest, but not the increase in flow required by the functionally loaded intestine. The clinical expression of the condition is called *intestinal angina*. Pathophysiologically, it is analogous with intermittent claudication and angina pectoris (Klein, 1921; Mikkelsen, 1957). The visceral pains that occur when meals are taken are attributed to anoxemia of the smooth muscles of the intestine (Dunphy, 1936).

Total occlusion

Sudden and total occlusion of the superior mesenteric artery or vein deprives the entire small intestine and half of the colon of the major part of the arterial flow or the venous drainage, respectively. Arterial occlusion was described by German surgeons during the first half of the nineteenth century, when Tiedemann reported a case in 1843. Subsequently, important contributions were made, with regard to its pathological anatomy, pathophysiology, clinical symptoms and therapy, by Klein (1921), Moore (1941), Rives *et al.* (1948), Mikkelsen (1957), and Forty (1957) among other authors. The sudden and totally obliterative thrombosis of the superior mesenteric vein has been similarly discussed by Brown (1940), Moore (1941) and others.

The pathophysiological factors that mainly determine the fate of the intestine when its circulation has been arrested are:

1. The capacity of the collateral circulation.
2. The bacterial flora of the intestine.
3. Intravascular thrombosis peripheral to the occlusion level.
4. Intestinal vasospasm.
5. The degree of intestinal distension.

The collateral circulation has not sufficient capacity to supply the intestine when the main trunks are suddenly blocked. On the other hand, if vascular obstruction develops over a longer period, it can take over entirely the flow of the main trunks. This has been convincingly demon-

strated on arteries by Blalock & Levy (1939) and Lillehei *et al.* (1959). On the venous side there also exist collaterals that can take over very extensive venous drainage (Laufman, 1943; Brunschwig *et al.*, 1945).

The bacterial flora is of decisive importance for the possible survival of the intestine when the circulation has been interrupted. The idea of injurious effects of toxic substances in a small intestine with circulatory damage had its early advocates (Stone *et al.*, 1912; Cooper, 1928, among others). It was assumed that these substances were of bacterial origin (Davis & Stone, 1917; Dragstedt *et al.*, 1917). Decisive experimental proof of this theory was presented by Sarnoff & Poth (1944), and Sarnoff & Fine (1945). They showed that sulfasuxidine had a protective effect on the intestinal wall after occlusion of the mesenteric vein. This was a verification of the bacterial factor in intestinal damage; and corresponding results were reported in respect of penicillin (Harper & Blain, 1945; Blain & Kennedy, 1946), streptomycin (Davis *et al.*, 1948), and tetracyclines (Lillehei *et al.*, 1959; Barnett, 1960; Cohn *et al.*, 1960; Cohn & Atik, 1961). Thus, the reduction of the rapidly increasing bacterial flora in the intestine decreased the absorption of lethal toxins and prevented the bacterial invasion of the ischemic intestinal wall. Endotoxins are produced by a number of gram-negative bacilli (Barnett, 1960; Turner *et al.*, 1961; Yull *et al.*, 1962; Amundsen & Gustafsson, 1963). Another factor of protein nature which is derived from the ischemic intestinal wall increases the toxicity of the intestinal content (Amundsen & Midtvedt, 1964 and Amundsen, 1964).

Intravascular thrombosis peripheral to the occlusion level is an early phenomenon. It is preceded by sludge in the small veins (Martin *et al.*, 1949). Especially in venous occlusion, sludge and microthrombosis are pronounced, and consequently, intravascular thrombosis is of great significance with regard to the rapid destruction of the intestinal wall (Robb *et al.*, 1965).

These processes can be counteracted by heparin (Nelson & Kremen, 1950; Robb *et al.*, 1965), which, it has been stated, may even recanalize the thrombi and stimulate the formation of collaterals (Loewe *et al.*, 1947). Anticoagulants and other remedies that promote flow, such as low-molecular dextran can assist in obtaining such

respite as will enable the collateral circulation to take over.

Intestinal vasospasm always occurs in the vascular area of the occluded vascular trunks. The phenomenon has been investigated by Laufman & Method (1947) and Laufman *et al.*, (1948). The effect of venous occlusion was in these respects more pronounced. Peripheral vasospasm may be assumed to be of decisive importance for the microcirculation and for the occurrence of sludge, microthrombi, and thrombosis.

Intestinal distension is especially important in those cases where the circulatory disturbance is due to strangulation of a loop (Barnett, 1960; Cohn *et al.*, 1960; Cohn & Atik, 1961). Distension further reduces the blood flow of an intestine whose circulation has been severely damaged (Scott & Wangenstein, 1932; Wangenstein, 1937). The combination of anoxemic intestinal wall, bacterial intestinal content and distension is unfavourable for the organ's chances of survival.

The surviving intestine

After severe circulatory disturbance with surviving intestine, its functions will often be affected. Loss of normal motility, with intestinal paralysis, was already described by Councilman (1894) and has been confirmed experimentally by Laufman (1950). Raw (1943) introduced the term *physiologic stricture*. (See also Reich, 1913; Davis, 1921; Garcia, 1927.) Loss of mucosal function can, in a similar way, cause malnutrition (Ortner, 1903; Klein, 1921; Dunphy, 1936; Berman & Russo, 1950). Finally, changes in the intestinal wall may give rise to such scar formation that stricture occurs (Garré, 1892; Ginzburg & Klein, 1928; Ginzburg & Oppenheimer, 1933; Barry, 1942; Raw, 1943; Hurwitt *et al.* 1953, and others). Another sequela, in relation to the collateral vessels' capacity to compensate for the lost blood supply, is the susceptibility to failure in the *central* circulation. This was pointed out as early as 1854 by Virchow. In this connection such conditions as cardiac insufficiency, haemorrhagic shock, dehydration, etc. are well known (Moore, 1941).

Peripheral Vascular Occlusion

The occlusion of small vessels at and distal to the mesenteric arches is possibly more common than central occlusions. By means of experimen-

tally induced obstruction of peripheral mesenteric vessels, Boley *et al.* (1965) were able to produce changes in the small intestine which closely resembled characteristic diseases. They consider that such peripheral vascular damage is of decisive importance for the development of certain chronic intestinal diseases such as regional enteritis and ulcerative colitis.

GASTROINTESTINAL MOTILITY

General Principles

The transport of solid and liquid contents through the gastrointestinal tract occurs exclusively in a downward direction. Bayliss & Starling (1899) explained this principle with their classical "law of the intestine: Excitation of any point of the gut produces contraction above and inhibition below". Later Cannon (1939) called this mechanism a "myenteric reflex". The stomach empties its contents, with a rhythmic peristalsis, into the duodenum, and from there the food is rapidly transported through the upper part of the small intestine, but subsequently it proceeds more and more slowly.

The motor activity has three characteristics, namely, tonus, rhythmic contraction, and peristalsis. The first is a static contraction of smooth muscle fibers maintained without fatigue, and normally liable to frequent changes. The rhythmic contraction mixes the contents and creates the necessary conditions for effective digestion and absorption. Finally, the peristaltic activity is superimposed on the other functions and has, in the proper sense of the term, a propulsive character.

Our knowledge of the motor functions has been substantially augmented during recent years owing to the introduction of new methods of recording. The intestinal movements can be directly visualized by conventional roentgen technique, but especially by cineradiography (Texter *et al.*, 1958). A great advance is due to the technique of continuous recording of intraluminal intestinal pressure. This can be done indirectly by transmitting the pressure via a balloon in the intestinal lumen (balloon method) or directly with pressure transducers of different kinds (Hightower, 1959), among these the pressure sensitive radiotelemetering capsules (Farrar *et al.*, 1957; MacKay & Jacobson, 1957).

Emptying of the Stomach

The stomach serves as a reservoir for solid and liquid food; it mixes its contents so that they become available for secretion, and, finally, empties them into the duodenum. It utilizes mixing and peristaltic types of motility with varying tone; all of which can be defined by the variations in the intraluminal pressure which they cause in the organ. It is the peristaltic activity in the region of the antrum which produces the pressure gradient that empties the contents of the stomach into the duodenum. The emptying occurs in accordance with a definite pattern, which is known through experiments with test meals. It has the character of an exponential function, so that a definite part of the contents leaves the stomach per unit of time. The principle was first described by Marbaix (1898), and has subsequently been verified by Enríques de Salamanca & Picazo (1942), Hunt & Spurrell (1951), Hawkins *et al.* (1953). It also seems to apply to different experimental animals such as the dog (Tamarit & Enríquez de Salamanca, 1952), and the rat (Reynell & Spray, 1956; Rosenthal & Nasset, 1958; Derblom, Johansson & Nylander, 1963; Sögnen, 1965).

Motility of the Small Intestine

The functions of the small intestine are intimately correlated, so that the motor activity creates optimal conditions for secretion-digestion and absorption. Like the stomach, the small intestine has a differentiated motor pattern, which, in principle, varies the tonus, mixes the contents and drives them forward (Code *et al.*, 1952, 1957). Propulsion is essentially the result of peristaltic activity. Normal transport downwards in the intestine, which is most rapid in its upper part and gradually becomes slower farther down, was explained by Alvarez (1948) as dependent upon gradients of motility. This theory has been criticized by Thomas (1955) who asserted that the polar conduction in the intestine is dependent on the integrity of the myenteric plexus. This, and not the smooth muscle layers, generates and supplies regular impulses. As yet, however, much is still obscure concerning peristalsis. Thus, we do not know how it is initiated, the cause of its polarity downwards in the intestine or why its frequency diminishes in a distal direction.

In the small intestine an initially rapid, and

in its distal parts an increasingly slower propulsion of the contents corresponds to the exponential course of the emptying of the stomach. This relation between the emptying of the stomach and the propulsive motility of the small intestine was suggested by Cummins & Jussila (1955), and Aberdén *et al.* (1960). Their opinions were based on roentgenological observations. Direct quantitative analysis of the correlation has been made by Grevsten, Johansson & Nylander (1967), and Johansson & Nylander (1968). The correlation was found to hold good for the larger part of the small intestine that transports the contents at the same rate as they are delivered from the stomach, whereas, at an earlier stage, the most distal parts are propulsively less active. Later, also here propulsive activity takes place so that the contents are passed into the cæcum. The ileo-cæcal transit proceeds along a linear course, so that during the relevant period a constant amount of the contents is emptied per unit of time.

Chapter II. The Problem

Ischemia in the small intestine provokes spasm in its smooth muscles (Rives *et al.*, 1948). Its clinical expression in mesenteric vascular occlusion is colicky pains at a stage where irreversible intestinal damage has not yet occurred (Meier & Waibel, 1964). According to Sidky & Bean (1958) such initial muscle spasm probably is a threat to the collateral circulation in the intestinal wall. On the other hand, it is not known whether or how such increase in tonus affects the propulsive motility of the intestine. Laufman (1950) possibly gave an indication in this direction, when he showed that an ileum loop lost its natural peristalsis after venous occlusion of such short duration that the loop was not damaged irreversibly. A corresponding clinical condition was described by Moore (1941), who observed, in a case of mesenteric vascular occlusion, that the collateral circulation could be sufficient to keep the intestine viable, but not to maintain its normal peristalsis.

The exceptional protection of the small intestine against vascular occlusion applies primarily to the mucosa. As has been previously mentioned, its blood supply and exchange surface are poten-

tially very large, while the smooth muscle layers correspond essentially to the skeletal muscle in these respects (Folkow, 1967). Thus it is only reasonable that an interruption in the blood supply should affect more severely the smooth muscles and their intrinsic plexuses.

Previously, the effects of a central interruption of the mesenteric blood flow were mainly studied. The changes in the intestinal wall when the *small* vessels are obstructed at and distal to the last arches has not aroused a similar interest. As was previously pointed out, Boley *et al.* (1965) showed that such interruption in the circulation can give rise to intestinal damage which is characteristic of chronic intestinal diseases.

No investigations that have systematically analyzed the propulsive motility of the gastrointestinal tract, with various degrees of ischemia in the intestinal wall, have been reported hitherto.

Our problem was, therefore: *How was the emptying of the stomach and the propulsive motility of the small intestine affected when a section of it was subjected to standardized and graded surgical ischemia?*

Chapter III. The Experimental Animal and Relevant Characteristics of its Gastrointestinal Tract

The essential parts of the experimental technique that was used in this investigation required an extensive animal material. Hence it was desirable to choose a small, inexpensive experimental animal. We had previously used the albino rat in a series of similar investigations and were familiar with the anatomical and physiological characteristics of its gastrointestinal tract.

The rat *stomach* has two distinct parts, the *cardiac* and the *pyloric* portion. The former, the upper part of the organ, has a thin, transparent wall lined with squamous epithelium and two very thin smooth muscle layers. This part performs the stomach's function of acting as a reservoir. The *pyloric* portion on the other hand, has active glandular epithelium and well-defined strong muscle layers. The anatomical structure corresponds to its secretory and motor activity.

The *small intestine* has no anatomical char-

acteristics that in principle distinguish it from the human small intestine. The number of intestinal arteries varies between 15 and 19, with a mean of 16 (Weyrauch & De Garis, 1937). Proximally they come off from the main trunk at shorter intervals than further down. Thus, in the terminal ileum each intestinal artery supplies a longer segment of the gut than higher up. They ramify during their course to the mesenteric border of the intestine. Branches from consecutive arteries unite to form primary arches of which the jejuno-ileal mesentery has about 45. These give rise to a second generation of arches from the convexity of which straight arteries proceed to the mesenteric attachment of the intestine. The fork-like ramification between two consecutive secondary arches will in the following be called a *mesenteric end arcade*.

Chapter IV. General Aspects of the Material and the Operation Technique

The material consisted of 906 white laboratory rats belonging to the same strain (Sprague-Dawley), and all males. They were not used for at least one week after delivery. They were given a diet fully adequate in respect to calories, minerals and vitamins (EWOS-Södertälje).

Before the experiments the animals were deprived of food for 18 hours, but had free access to water. For all the operative procedures the

animals were anaesthetized with ether. Anaesthesia was induced, by placing the animals in closed glass containers with gauze compresses soaked in ether, and then maintained with a minimum of ether on an open mask. The animals were conscious when the operation was finished.

The operative technique was carried out under clean but not sterile conditions.

Chapter V. Standardized and Graded Ischemia in a Segment of the Small Intestine

METHOD FOR OBTAINING THE ISCHEMIA

From the morphological description it is evident that the intestinal vessels of the rat anastomose reciprocally to form two sets of arches. The fork-shaped connection between two adjacent secondary arches has been called a *mesenteric end arcade*. The term arcade may possibly be considered inappropriate, since the concept sometimes is used for the vascular arches. The designation, abbreviated to *mes end arc* can hardly be misunderstood, however, and adequately covers the vascular section in question.

Standardized and gradually increased ischemia was obtained by ligating an increased number of such mes end arc. The ligature was invariably made immediately proximal to the point of division (Fig. 1) and with 5-0 cardiovascular silk (Ethicon). The first and most distal ligature was made around the seventh mes end arc counting from the ileo-caecal junction, and from there a further given number of ligatures were made in a proximal direction. Thus, the central part of the devasculated intestinal loop was displaced proximally, owing to the increasing number of ligatures.

QUANTITATIVE EVALUATION OF THE ISCHEMIA

The number of ligated mes end arc constituted an *anatomical* measure of the surgically-induced ischemia in a segment of the small intestine. It was desirable, however, to correlate this graduation with a more exact quantitative assessment of the blood flow. The principle of measuring the passive absorption=diffusion from an intestinal loop of a radioactive substance, as an indirect expression of its effective exchange circulation, was regarded as suitable.

Material and Methods

In all, 142 animals were used for this part of the investigation. All of them received 5 drops of

an 0.33% iodide solution (NaI) per 100 ml of drinking water. According to the experimental measures, the material was divided into nine experimental groups. As controls, animals were used which had only been laparotomized (laparotomized controls; LC).

Otherwise, grouping was determined by the number of mes end arc that were ligated. The experimental groups were named according to this principle, and the number of ligated mes end arc was varied between 3 and 15. In order to estimate the maximal error that might occur when the radioactive test substance passed out through the intestinal wall whose circulation had been damaged, an experimental group with a totally devasculated intestinal loop (*tot devasc*) was included. Table I shows the division of the material into experimental groups, the number of animals in each group and the mean body weight.

Radioactive sodium iodide (Na I^{131}) was used as the test substance. The original solution was diluted so that 0.10 ml contained 10 μCi when the experiment was begun. Carrier was added, so that the specific activity was 30 μCi per 100 μg of iodide. For each experiment 0.10 ml was used, which was measured with weighed tuberculin syringes with a calculated accuracy of $\pm 5\%$. The radioactivity of the dose was recorded for each individual experiment.

The radio-iodide was injected into a central loop of the partly devasculated intestine, which was closed off by ligation from the continuity of the intestine. The length of this loop corresponded to 2 mes end arc. The ligatures (5-0 cardiovascular silk) were placed so that they did not interfere with the vascularity along the mesenteric attachment (Fig. 2 a). In the LC-group the dose was injected into an intestinal loop of the same length, which was separated by ligatures in the same way. The distance from the ileo-caecal angle corresponded to 10 mes end arc.

In the group *tot devasc*, the corresponding intestinal loop was doubly ligated, and was cut

TABLE I. *Characteristics of the material*

Experimental group	n	Weight in g		
		Isol. loop	Stomach	Body
LC	26	0.6±0.04	3.2±0.12	231±3
3 mes end arc	15	0.9±0.04	2.9±0.05	324±6
5 mes end arc	15	0.8±0.06	3.1±0.09	314±13
7 mes end arc	15	0.8±0.05	3.2±0.12	310±5
9 mes end arc	15	0.9±0.07	3.2±0.13	340±4
11 mes end arc	15	0.7±0.08	2.8±0.09	260±4
13 mes end arc	16	0.8±0.06	3.4±0.22	255±7
15 mes end arc	15	0.8±0.08	2.6±0.25	229±9
Tot devasc	10	0.3±0.09	2.9±0.24	214±3

off from the intestinal continuity and mesenteric connections. Thus, the loop was allowed to lie free in the abdominal cavity (Fig. 2 *b*).

Injection of the radioactive dose was made with a fine bore needle (Record No 16), after it had been ascertained that the point of the needle was free in the intestinal lumen. Following injection and withdrawal of the needle, dry filter paper was put on the insertion site. Control measurements showed that it did not contain any radioactivity in excess of the background level.

After a given number of mes end arc were ligated and before radio-iodide was deposited in the loop, the pylorus was shut off with a ligature (5-0 cardiovascular silk) (Fig. 2). The abdomen was closed, and the animal had awakened from the anaesthesia when the last sutures were sewn.

The animal was put in a specially constructed cage (Fig. 3); its tail was effectively screened off from its body and wholly enclosed in a lead container provided with a hole. The tip of the scintillation detector was fitted exactly over this hole when the tail portion of the cage was introduced into the scintillation detector's lead container. The distance between the surface of the tail and the tip of the detector was 1 cm. The detector was connected to a recording unit with an automatic, linear recorder. Thus, the occurrence of radioactivity in the tail could be recorded continuously as a function of time. The graph was called the *tail curve* (Fig. 4). It had a linear course during the experimental period and could consequently be characterized by the tangent of the angle of inclination. The method was previously described by Derblom & Nylander (1963) and Derblom, Johansson & Nylander (1963).

After the recording had been completed the

experimental animal was killed with ether. The abdomen was opened, the stomach doubly ligated at the cardia and below the pylorus and removed separately, as was also the isolated intestinal loop in which the dose had been deposited. The preparations were weighed and the radioactivity recorded in each one of them (Fig. 2). Each recording was made twice, and not less than 10,000 impulses were counted. In the same way the radioactivity in the body of the animal was determined, which was thus without its stomach and intestinal loop.

Discussion of method

The elimination, from the intestinal loop, of a water-soluble and diffusible substance takes place over the exchange vessels of the mucosa. It is dependent *mainly* on two factors

1. The concentration gradient, in respect of the substance, between the lumen of the intestine and the capillary blood.
2. The size of the contact area between the solution and the capillary blood, which, in turn, depends partly on the size of the available mucosal area and partly on the blood circulation in the latter.

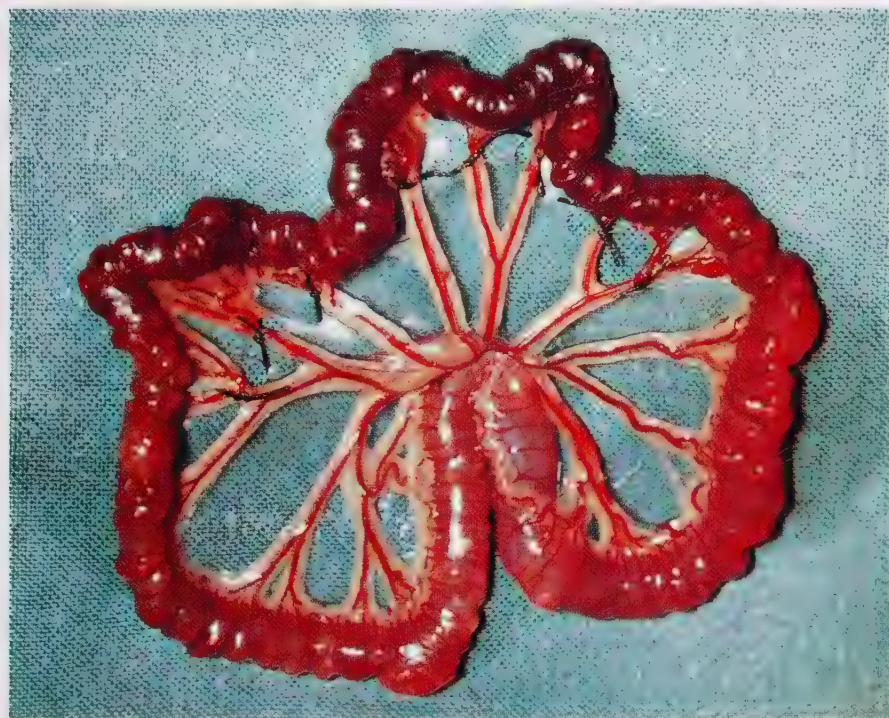
Note 1: The test solution was the same, with unchanged iodide concentration in all the experiments. Moreover, there was no reason to assume that the iodide metabolism varied between the different experimental animals. Particular care was taken with regard to the homogeneity of the material; and all the animals were given iodide in their drinking water.

Note 2: The isolated intestinal loop, in which the radio-iodide had been deposited, was always the same size and corresponded to the distribution of two mes end arc. The loop was always empty, like the rest of the intestine. Table I shows that there was good agreement among the groups with regard to the weight of the loop. Its weight in the LC-group was slightly less. This was probably due to the fact that the blood supply of the intestinal wall was not disturbed as it was in the other groups, where it is likely that oedema and bleeding increased the weight. In the tot devasc group the weight was remarkably low, probably owing to loss of fluid to the surroundings.

The isolated loop was always situated *centrally* in the devascularized intestinal area. Absorption



a



b

Fig. 1. Appearance of the small intestine 30 minutes after the ligation of 7 (a) and 15 mes end arc (b). Ligatures are made immediately proximal to the vascular ramifications which, upwards and downwards, feed the

secondary arches. The cyanotic discoloration of the intestine, and its contracted condition are most apparent when 15 mes end arc are ligated (b).

Direct registration of radioactivity
after 30 min.

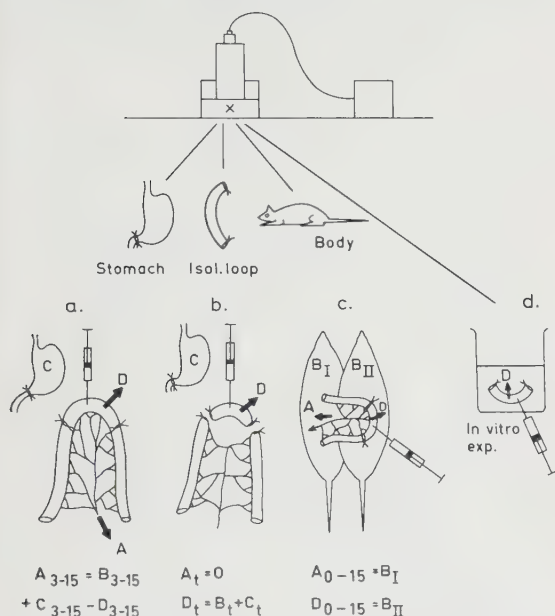


Fig. 2. Schematic representation of the experimental design. The radioactive dose is deposited in the isolated loop according to alternatives a-d. (a) 3-15 mes end arc ligated; (b) total devascularization; (c) "double-rat" experiment with 0-15 mes end arc ligated; (d) in vitro experiment.

Radioactivity was recorded in the isolated stomach (C), the isolated loop, and in the rat body exclusive of these parts of the gastrointestinal tract (B).

A = absorption over the exchange vessels of the loop. D = transmural leakage from the loop (in alternatives a-c = peritoneal absorption). See also text.

from this area should be the least, since both the proximal and the distal anastomotic vessels have the least possibility of providing for the flow.

Consequently, the experimental measures applied for obtaining a constant concentration gradient for the iodide, and constant size of mucosal area may be regarded as reliable.

Elimination of the test solution is finally dependent upon such changes in blood flow of the mucosa as are determined by the total capillary exchange surface. The effects on the splanchnic circulation, which were caused by anaesthesia, operations, and other experimental measures, were the same for the entire animal material; all the measures were strictly standardized. Hence, only effects directly connected with mesenteric vascular occlusions differentiated the groups from one another. Consequently, the elimination of ra-

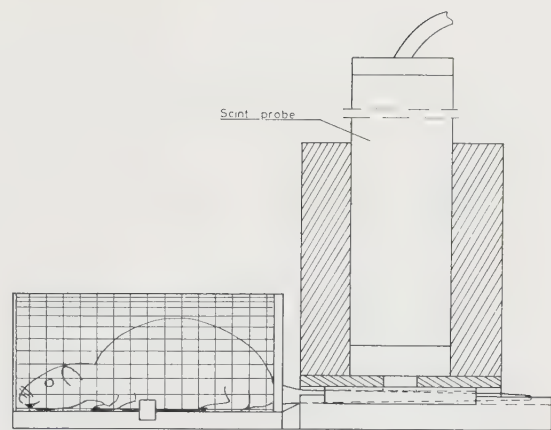


Fig. 3. Experimental arrangement used to record the radioactivity appearing in the rat tail-tail curve. For description, see text.

dio-iodide from the loop of the small intestine, which was always the same size, is probably an indirect expression of the mucosal blood circulation in the respective experimental groups.

In the presence of a negative iodide balance the thyroid gland collects iodide from the blood against a high concentration gradient. In this experimental series the thyroid gland was saturated in this respect, as the animals were regularly given

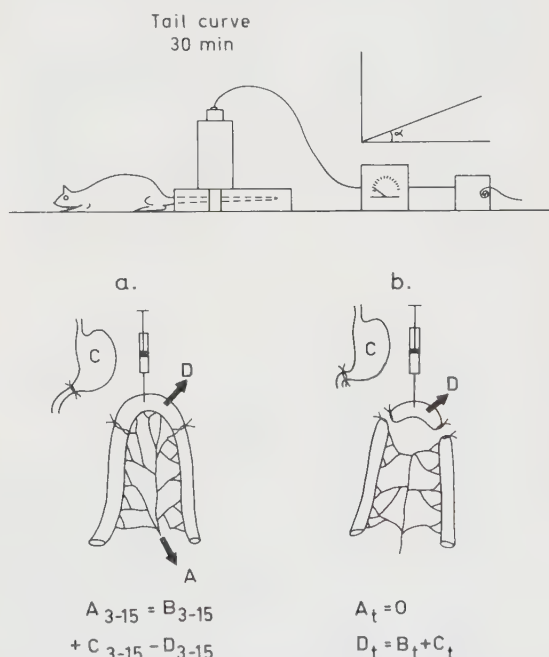


Fig. 4. Schematic illustration of the recording of the tail curve in alternatives a and b. The tail curve is given as the tangent of the angle of inclination (α).

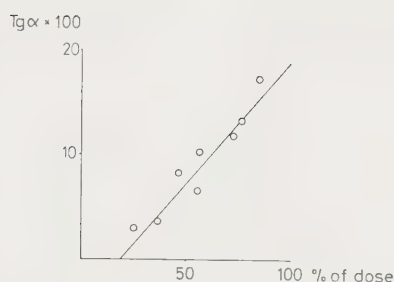


Fig 5. Correlation between the tail curve (tangent of the angle of inclination $\times 100$ —vertical axis) and the absorption from the isolated loop (per cent of the dose—horizontal axis) in all the experimental groups. The regression line is adjusted to the material according to the least squares method. $y = 0.23 x - 4.3$.

iodide in their drinking water. In all the groups the thyroid gland also lacked significant radioactivity 30 minutes after the radioiodide had been deposited in the loop.

The secretory cells of the gastric mucosa also take up iodide in the same way and then secrete it. In these experiments the secretion was trapped behind the pyloric ligature and the radio-iodide was recorded. Thus, it was possible to ascertain whether the surgically induced ischemia in a loop of the small intestine could possibly influence the iodide secretion of the stomach.

During 30 minutes a significant part of the radio-iodide was not excreted over the kidneys. This was previously demonstrated by Derblom, Johansson & Nylander (1963), who, even after 60 minutes, did not find any radioactivity in the

TABLE II. Percentile distribution of the radioactive dose (NaI^{131}), in the experimental animal, 30 min after its deposition in the isolated intestinal loop

Mean values with S.E.

Experimental group	n	Isol. loop	Stom-ach	Body	Total absorption
LC	26	15 ± 2.0	11 ± 0.9	74 ± 1.9	85
3 mes end arc	15	27 ± 3.1	6 ± 0.4	67 ± 2.8	73
5 mes end arc	15	24 ± 1.9	9 ± 0.8	67 ± 1.9	76
7 mes end arc	15	43 ± 2.9	5 ± 1.4	52 ± 2.6	57
9 mes end arc	15	45 ± 2.9	5 ± 0.3	50 ± 2.7	55
11 mes end arc	15	53 ± 3.8	4 ± 0.7	43 ± 3.4	47
13 mes end arc	16	63 ± 1.9	2 ± 0.3	35 ± 1.9	37
15 mes end arc	15	75 ± 1.8	3 ± 0.3	22 ± 1.7	25
Tot devasc	10	84 ± 2.1	2 ± 0.3	14 ± 1.8	16

collected urine of the bladder. Nor had the rat's salivary glands taken up any measurable amounts of the radioactive dose during this period.

The tail curve, which was obtained by the continuous recording of the radioactivity occurring in the rat tail, was used as an *indirect* expression of the elimination of the radio-iodide from the isolated intestinal loop. For the most part, the cross section of the tail consists of supporting tissues, and the blood is only an insignificant part. Thus, the recorded course represented the occurrence of the radio-iodide in the *extravascular space*, which was previously demonstrated by Derblom, Johansson & Nylander (1963).

Its reliability as an indirect expression of iodide absorption from the standardized intestinal loop is shown in Fig. 5, where the tangent of the angle

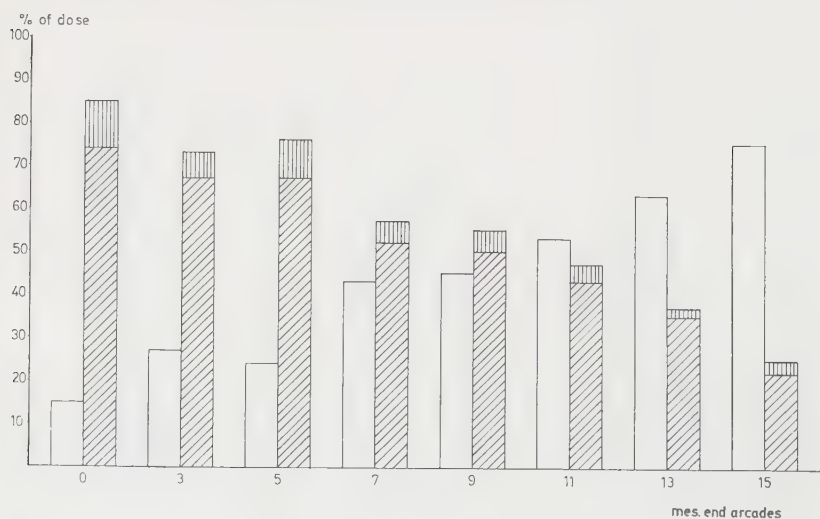


Fig. 6. Histogram representing the distribution of the radioactive dose in the isolated loop (hollow rectangle), the isolated stomach (vertically dashed rectangle), and the remainder of the rat body (obliquely dashed rectangle). The two last-mentioned indicate the total absorption. The height of the rectangles indicates the percentages of the dose. The number of mes end arcades is given on the horizontal axis.

of inclination is plotted against the percentage values of the total iodide uptake in all the experimental groups (correlation factor = 0.97).

Results

Table II and Fig. 6 show the percentile distribution of the radioactive dose in the different specimens (see Fig. 2).

- 1. *The isolated loop* of the small intestine = un-absorbed part of the dose
- 2. *The stomach* = absorbed part of the dose which was secreted and trapped in the isolated organ
- 3. *The animal body* = rest of absorbed part of the dose.

The sum of the two last recordings represented the total absorption from the intestinal loop. The *tail curve* was expressed by the tangent of the angle of inclination. The results are shown as the means of the given number of observations with standard error. They are presented in Fig. 7.

In the LC-group the isolated loop had retained 15% of the radioactive dose after 30 minutes, total absorption was 85%, and 11% had been secreted and trapped in the stomach. With an increasing number of ligated mes end arc absorption from the loop diminished. Already when 3 mes end arc had been ligated, the uptake had decreased, and nearly twice as much remained in the loop (27%). Only 6% had been secreted by the stomach. The tendency for an increasingly larger part of the dose to remain in the loop and an increasingly smaller part in the stomach was, as seen in Fig. 6, noticeable, even if differences might be lacking between groups closely related from an experimental point of view. The extreme

TABLE III. *Per cent of the absorbed radio-iodide that is secreted and trapped in the pylorus-ligated stomach during the experimental period*

Experimental group	n	% of total absorption trapped in the isolated stomach
LC	26	13
3 mes end arc	15	8
5 mes end arc	15	12
7 mes end arc	15	9
9 mes end arc	15	9
11 mes end arc	15	9
13 mes end arc	16	5
15 mes end arc	15	12
Tot devasc	10	13
		Mean = 10

TABLE IV. *Tail curve inclination (tg. angle of inclination)*

The curve is linear during the experimental period (30 min). Mean values with S.E.

Experimental group	n	Tail curve (tg. inclin. angle)
LC	26	0.173 ± 0.008
3 mes end arc	15	0.119 ± 0.007
5 mes end arc	15	0.134 ± 0.007
7 mes end arc	15	0.104 ± 0.008
9 mes end arc	15	0.067 ± 0.006
11 mes end arc	15	0.082 ± 0.007
13 mes end arc	16	0.035 ± 0.005
15 mes end arc	15	0.029 ± 0.003
Tot devasc	10	—

group, 15 mes end arc, had retained 75% of the dose at the end of the experimental period. Of the 25% that were absorbed, 3% had gone to the stomach. The tot devasc group, with the isolated loop free in the peritoneal cavity, had lost 16% from the loop, 2% of which had gone to the stomach.

When the gastric secretion of the radio-iodide was expressed *in per cent of the absorbed part*, it proved to be strikingly constant. Table III shows that the gastric secretion of iodide was then between 5 and 13% of the radio-iodide that the animal had absorbed. There was no relation between the iodide secretion and the number of

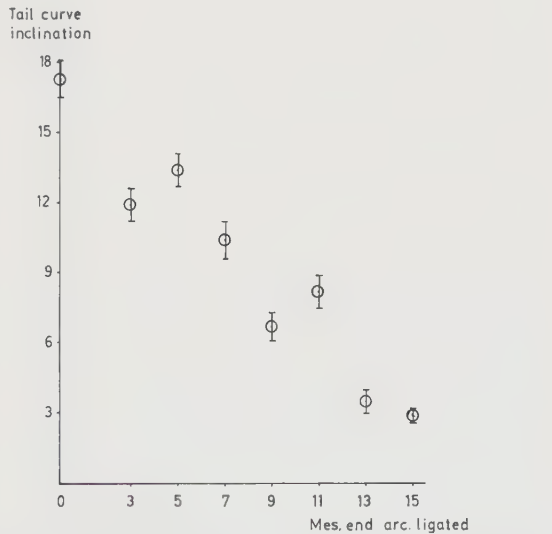


Fig. 7. Tail curve expressed as the tangent of the angle of inclination × 100 (vertical axis) in the different experimental groups (identified with the number of ligated mes end arc according to the horizontal axis).

mes end arc ligated. Thus, the value for the LC-group was 13%, and identical with the extreme groups 15 mes end arc and tot devasc. The group 13 mes end arc followed a somewhat different pattern and had the lowest value of the series (5%).

The slope of the *tail curve* diminished correspondingly when an increased number of mes end arc were ligated (Table IV, Fig. 7). In the LC-group the mean value was 0.173 and in the group 3 mes end arc it was reduced to 0.119. The extreme group 15 mes end arc had minimal inclination (0.029). In the tot devasc group there was no radioactivity at all over the tail, during the experimental period.

Discussion

Absorption of radio-iodide from the isolated loop decreased the more, the greater the number of mesenteric vessels that were shut off. The iodide is absorbed passively over the membranes between the lumen of the intestine and the blood in the exchange vessels. From the discussion of the method on p. 17 it was evident that the decisive factor was essentially standardized as being *the gradual reduction of the total exchange area obtained when an increased number of mesenteric vessels are shut off*.

There was good agreement between the direct measurements and the continuous recording of the *tail curve*. The latter, which was regarded as an expression of the occurrence of radio-iodide in the extravascular space, is thus a good indirect indicator of iodide absorption from the intestinal loop and from its available capillary bed.

If the blood flow to the small intestine is reduced, it can, to some extent, be compensated for. Folkow (1949) showed that when pressure or flow decreases, the myogenic tonus is reduced in the precapillary resistance vessels of the intestinal mucosa. Bean and Sidky (1957) observed similar vasodilatation when they perfused with blood with low oxygen tension. Johnson (1960), Johnson & Hanson (1962), and Hanson & Johnson (1962) have subsequently shown that the capillary area of the intestinal mucosa is protected against disastrous fall in pressure not only through the decrease in precapillary resistance, but also through increase in postcapillary resistance. In the former case, a *myogenic* reflex is active, and in the latter, a local, *sympathetic*, *axon*

reflex, with receptor on the arterial and effector on the venous side of the capillary area (Hanson & Johnson). When the limits of the compensatory capacity are exceeded, in the first place, the intestinal functions requiring most energy are reduced. Guthrie & Quastel (1956) found that anoxia, following mesenteric vascular ligatures and experimental shock, reduced absorption which required energy (glucose, fructose, amino acids), whereas passive absorption (sorbitol) remained intact. These results were essentially verified by Varró *et al.* (1965, 1967 *a* and *b*), who observed better utilization of the oxygen of the arterial blood, resulting in an increased arterio-venous oxygen difference.

Thus, previously, such a degree of anoxia in the small intestine as to affect the passive absorption had not been obtained. All the reports mention more or less short and relatively central closures of the mesenteric vessels. In view of the potential capacity of the intestinal mucosa to compensate for the reduced flow and of the fact that the passage of iodide from the lumen of the intestine to the blood stream is a passive process, there is reason to assume that serious disturbances in the blood supply of the intestine are required before the iodide uptake is affected. In our experiments the vessels were ligated rather close to the mesenteric attachment of the intestine, so as to have to deal with the smallest possible number of anastomoses. The reduction in radio-iodide absorption, which was observed to correspond to the surgically produced ischemia, affected, therefore, an intestinal loop where compensatory changes in the capillary flow could hardly any longer be of significance.

When a large number of end arcades have been ligated, the question arises whether the iodide could have possibly diffused through devitalized mural layers to the peritoneum and have been absorbed from there. The totally devascularized loop lost 15% of the dose during 30 minutes in this way. Of the radio-iodide absorbed peritoneally, 2% went into the gastric secretion. Hence, the possibility could not be excluded, that the extreme group 15 mes end arc lost some undefined part of the dose through a devitalized intestinal wall. The results did not afford any definite information on this. Consequently, it was necessary to analyze the material more closely in this respect.

Chapter VI. Transmural Loss of Radio-iodide from the Isolated Intestinal Loop — “Double-rat” Experiment

MATERIAL AND METHODS

The material consisted of 23 pairs of animals divided into two experimental groups, LC and 15 mes end arc (Table V).

Operative technique (Fig. 2 c). Each experiment was made with 2 animals, *rat I* and *rat II*.

Rat I was operated on according to the corresponding experimental group in the preceding series. After 15 mes end arc had been ligated in the one group, the intestinal loop was chosen, which had previously been defined with regard to size and position. In both groups it was isolated by ligatures from the intestinal continuity.

Rat II was laparotomized with a small incision in the lower median line and placed close against the former. Adhering borders of the wounds were united to form the posterior wall of a small connection between the animals' peritoneal cavities.

Radio-iodide was injected into the isolated intestinal loop (*rat I*). The loop was deposited and fixed in the peritoneal cavity of *rat II*. The anterior wall of the connection between the animals was closed and light ether anaesthesia was maintained for 30 minutes. The animals were killed with ether and separated. The isolated loop was removed and the radioactivity in it and in each rat's body was recorded.

Discussion of the Method

With this experimental design it was possible, as previously, to determine the amount of radio-iodide that had left the loop during 30 minutes. The radioactivity recorded in *rat I* was the part of the dose that had left the loop through passive absorption and had been appropriated by the animal via the mesenteric veins. On the other hand, the radioactivity in *rat II* could correspond only to the radio-iodide that had passed through the intestinal wall and had been absorbed from this rat's peritoneum.

Some factors should be taken into account.

1. Radio-iodide could contaminate the surface of the loop following injection, and from there be absorbed by the peritoneum. To control this source of error the radioactivity of a filter paper that had been placed over the insertion site was measured. The recordings were negative, and consequently leakage from insertion or other contamination could be excluded.

2. Radio-iodide that had leaked out through the intestinal wall could be transferred to the peritoneal cavity of *rat I* and absorbed from there. The connection between the two peritoneal cavities was narrow, however, and only wide enough to allow the loop and its mesentery to pass through. Moreover, the peritoneal cavity of *rat I* was always situated higher than that in *rat II* where the loop was deposited.

3. Finally, it is self-evident that the occurrence of newly established vascular connections between the two peritoneal cavities can be excluded.

Thus, without qualification, it could be stated that *the radioactivity measured in rat I represented exclusively absorption from the intestinal loop via the blood stream, and in rat II it represented absorption from the peritoneum of such radio-iodide as had leaked out through the wall of the intestinal loop.*

RESULTS

Table V shows the percentage distribution of the radio-iodide in the isolated intestinal loop and in the bodies of the rats. In the LC group about 20% of the dose remained in the intestinal loop after 30 minutes. In the preceding experimental series the corresponding value was 15%. Thus, in all, about 80% of the dose had been absorbed, and no significant amount was found in *rat II*.

In the group 15 mes end arc about 80% of the dose in the intestinal loop was not absorbed. *Rat I* had absorbed about 15% and *rat II* about 5% of the dose.

TABLE V. "Double-rat" experiment

Percentile distribution of the radio-iodide in the isolated intestinal loop and the two rats 30 min after its deposition in the loop of Rat I. Mean values with S.E.

Body I: 0 mes end arc ligated

Number of experiments	% of dose		
	<i>Isol. loop:</i> unabsorbed portion	<i>Body I:</i> vascular absorption	<i>Body II:</i> peritoneal absorption = leakage
10	22±3.8	76±3.7	1±0.1

Body I: 15 mes end arc ligated

Number of experiments	% of dose		
	<i>Isol. loop:</i> unabsorbed portion	<i>Body I:</i> vascular absorption	<i>Body II:</i> peritoneal absorption = leakage
13	81±2.4	14±3.0	5±0.7

DISCUSSION

During the experiments the animals were under light anaesthesia for 30 minutes, and this may have influenced the capillary flow in the splanchnic area, which determines the elimination rate of radio-iodide from the intestinal loop. This probably applies especially to group 15 mes end arc. It is known that normally, adequate collateral circulation may not prove sufficient when, for some reason, the central circulation fails (Moore, 1941). If in the group 15 mes end arc the anastomoses were sufficient to maintain a certain degree of vitality in the intestinal loop, and the anaesthesia caused the central circulation to deteriorate, the intestinal wall might have sustained further damage and, consequently, more radioiodide may have leaked out through its wall.

If the LC-group is compared with the corresponding group in the preceding series, it will be found that in the former just over 20% of the dose remained in the intestinal loop after 30 minutes, and in the latter series 15%. Thus, there was very good agreement. No appreciable leakage of iodide occurred through the intestinal wall, but the whole absorption took place via the exchange vessels in the intestinal loop.

When the group 15 mes end arc was similarly

compared, agreement between the experimental series was equally good. After 30 minutes the loop contained about 80% in this experimental series and 75% in the foregoing series. If, in general, there was any difference, this should probably be ascribed, as in the preceding case, to the ether anaesthesia that lasted 30 minutes and its effect on the circulation.

Thus, only 5% of the dose leaked through the intestinal wall and was absorbed peritoneally. Hence, the surgically induced ischemia for 30 minutes did not cause any extensive change in the vitality of the intestinal wall. This was remarkable in view of the fact that in this experimental group the intestinal loop became totally necrotic after a few days (Wikström, 1968).

In the group tot devasc in the preceding experimental series just over 15% of the dose escaped from the corresponding loop. Thus, in the group 15 mes end arc, in the double-rat series, only 1/3 of this transmural leakage occurred, which indicates that the blood circulation, centrally in the large devasculated part of the intestine, was not entirely unsatisfactory.

MATERIAL AND METHODS

The series comprised 30 animals which were divided into 5 groups according to the length of the experimental period. The composition of the material is shown in Table VI.

Laparotomy was performed, and that part of the small intestine was identified which was previously used as an isolated loop. It was ligated in the usual way and radio-iodide injected. The intestinal loop was removed and transferred to a beaker containing warm (37°C) physiologic Krebs-Ringer solution (Fig. 2 d). The radioactivity was measured, and the beaker then put in a water bath thermostated at 37°C , where, according to the definition for the respective experimental groups, it was kept from 5 to 30 minutes (see Table VI). The loop was then transferred to another beaker with Krebs-Ringer solution, after which the radioactivity was again recorded. The difference between the two recordings was expressed in per cent of the original dose.

RESULTS

In Table VI the mean values for each experimental group are given. Moreover, the individual values have been plotted in a coordinate system against the time periods of the experiments (Fig. 8).

Kept *in vitro* the originally intact intestinal loop lost about 5% of the dose during the first

TABLE VI. *In vitro* experiments

Transmural leakage of radio-iodide from the isolated intestinal loop. Intact rats. Mean percentile values.

Experimental period in min.	Body weight in g. Mean of 6 experiments	Leakage in % of dose Mean of 6 experiments
5	211	5
10	220	6
15	201	10
20	208	19
30	216	25

5 minutes. After 30 minutes the loss was approximately 5 times greater. Increase in the permeability of the intestinal wall to iodide, which occurred as a function of time when the loop was kept in a physiologic salt solution, agreed approximately with a linear function, as will be seen in Fig. 8.

DISCUSSION

The isolated loop of the small intestine corresponded in origin and size to that studied in the preceding section. Removed, and kept in physiologic saline solution, it thus lost, during 30 minutes, about 25% of its radio-iodide. When it was kept, instead, *intraperitoneally* in the host animal, only 15% of the dose leaked out and was absorbed from the peritoneum. This may be due to some of the following factors:

1. The intraperitoneal environment has better prerequisites for maintaining the vitality of the loop.

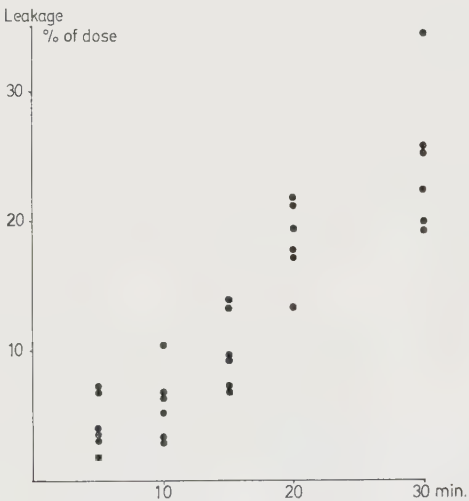


Fig. 8. Transmural loss of radio-iodide from the primarily intact loop *in vitro*. The leakage is expressed as per cent of the dose on the vertical axis, and the time in minutes that the specimen was kept in a physiologic saline environment on the horizontal axis.

2. Total devascularization of the loop in the peritoneum causes exudation of such material as reduces permeability (fibrin).

3. A combination of the two factors may be active.

The leakage of radio-iodide was insignificant during 30 minutes when 15 mes end arc were ligated (see "double-rat" experiments). This means that the recordings of the elimination of radio-iodide from the loop did really reflect the flow conditions of the exchange vessels and not the peritoneal absorption of radio-iodide which leaked out through the wall of the loop.

On the other hand, a peritoneal reaction can occur that renders the intestinal wall more impervious. Leakage which corresponds to the ischemic intestinal damage can thereby be reduced to an unknown extent. It seemed of importance to study this question further.

Chapter VIII. Permeability of the Ischemic Small Intestine to NaI^{131} *In Vitro*

MATERIAL AND METHODS

The material consisted of 51 rats and 5 experimental groups. The loop of the small intestine, previously defined with regard to its position and size, was isolated from the continuity of the intestine and the mesenteric attachments. In the IC-group this was done without any preceding measures. In the group LC-30 minutes the animals had been laparotomized 30 minutes earlier, and in the group LC-24 hours, this had been done 24 hours prior to the experiment. In the group 3 mes end arc—30 minutes, 3 mes end arc had been ligated in the mesentery of the loop 30 minutes earlier, and in the group 15 mes end arc—24 hours, 15 mes end arc had been ligated 24 hours before the experiment.

Table VII shows the experimental groups. The number and mean weight of the animals as well as the mean wet weight of the loop of the small intestine are also given.

Radio-iodide was deposited in the loop. The latter was excised and transferred to a beaker containing physiologic Krebs-Ringer solution warmed to 37°C and the radioactivity measured. After 15 minutes the preparation was put in another, identical environment, and the radioactivity was again recorded. This was repeated every 15 minutes, so that at the last recording the preparation had been kept 120 minutes *in vitro*. Hence, each preparation was recorded 8 consecutive times.

RESULTS

Loss of radio-iodide from the intestinal loop was expressed, as in the previous series, in per cent of the original dose. The results are presented in Table VIII, as mean values with standard error for all the experimental groups and periods; and in Fig. 9 they are plotted against the experimental periods of time in a coordinate system.

After 120 minutes the isolated loop had lost, in the IC-group, about 90% of the dose. The loss

was almost linear (Fig. 9) during the first 60 minutes, when about 15% left the loop every 15 minutes. Thus, after 60 minutes about 60% of the dose had leaked out. Subsequently, the intestinal isolate lost an increasingly smaller part of the dose during every 15-minute period.

Group LC-30 minutes had, for all the recordings, similar losses from the loop. With the exception of the value for 15 minutes, the leakage was throughout, however, somewhat less than in the IC-group (Table VIII). This condition is most clearly seen in the diagram in Fig. 9.

This tendency was accentuated in the group LC-24 hours. Already after 15 minutes leakage was less than in the foregoing groups, a condition that became more pronounced with every further 15-minute period. Thus, after 15 minutes the loss was about 10%, after 60 minutes about 45%, and after 120 minutes about 70% of the original dose (Table VIII). This retarded course, in comparison with the other experimental groups, is shown in Fig. 9.

In the group 3 mes end arc—30 minutes the intestinal loop had lost about 95% of the dose after 120 minutes. There was substantial loss during the first 60 minutes, when an average of 18% was lost during each 15-minute period, so that the loop had lost about 70% of the dose after 60 minutes. During the following 15-minute periods, when a further 25% passed through the intestinal

TABLE VII. *Characteristics of the material*

Experimental group	Pre-exp. interval		Number of experiments	Weight in g	
	min.	hrs.		Body	Isol. loop
IC	—	—	11	206 ± 3.0	0.7 ± 0.02
LC	30	—	10	215 ± 4.0	0.7 ± 0.03
LC	—	24	10	231 ± 13.5	0.7 ± 0.03
3 mes end arc	30	—	10	213 ± 8.0	0.7 ± 0.03
15 mes end arc	—	24	10	216 ± 3.4	0.8 ± 0.03

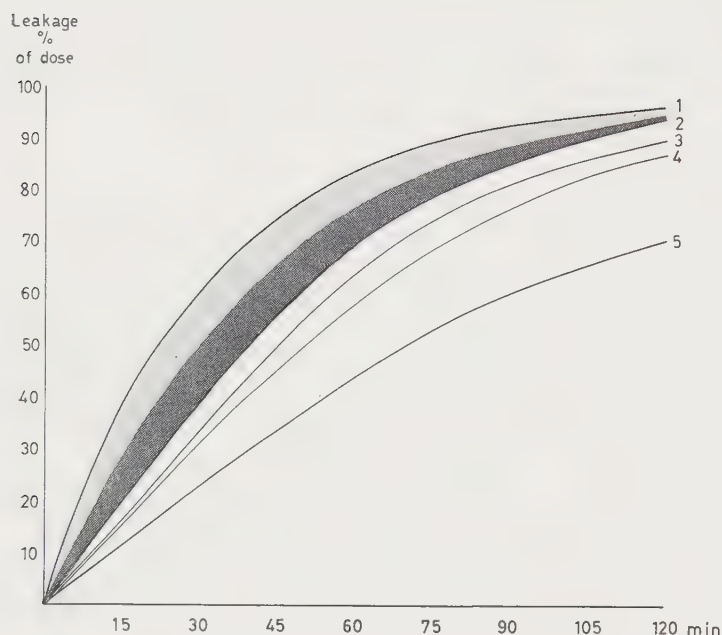


Fig. 9. The permeability to NaI^{131} *in vitro* of the surgically ischemic loop. Leakage is expressed in per cent of the radioactive dose (vertical axis) plotted against experimental time in minutes (horizontal axis). 1, Experimental group 15 mes end arc—24 hours; 2, Experimental group 3 mes end arc—30 minutes; 3, Experimental group IC; 4, Experimental group LC—30 minutes; 5, Experimental group LC—24 hours. Light shading=range of group 15 mes end arc—24 hours. Dark shading=range of group 3 mes end arc—30 minutes.

wall, this occurred with increasingly smaller loss per 15-minute period (Table VIII). In Fig. 9 the range of the group has been indicated.

In the group 15 mes end arc—24 hours practically the whole dose had left the intestinal loop after 120 minutes. As shown in Table VIII and Fig. 8 this loss took place earlier than in the foregoing groups. During the first 15-minute period already about 40% of the dose had passed out and during the following 15-minute periods a further 20%, 15% and 10% of the dose, respectively. The initially rapid course of this activity, which diminished more and more as the experimental period was prolonged, is demonstrated in Fig. 9.

DISCUSSION

The passage of the iodide from the intestinal loop to the physiologic saline solution was dependent mainly on two factors:

1. The concentration gradient between the two compartments and
2. The condition of the membranous system that the intestinal wall formed.

In these experiments the former factor was kept constant, since both the iodide solution and the physiologic saline solution had throughout a constant composition, with a fall in concentration for the iodide from the loop to the outer solution. As this was renewed every 15 minutes, from this point of view, the passage of the iodide over the

TABLE VIII. *In vitro* experiments

Transmural leakage of NaI^{131} from the isolated intestinal loop under different experimental conditions. The values are given in per cent of the radioactive dose. Mean values with S.E.

Experimental group	Pre-exp. interval		Experimental period in min.							
	min.	hrs	15	30	45	60	75	90	105	120
IC	—	—	14±1.3	33±2.6	50±2.8	63±3.1	74±3.2	81±2.6	86±2.4	89±2.2
LC	30	—	16±1.0	30±1.7	45±1.9	59±1.8	69±1.8	77±1.7	83±1.4	87±1.4
LC	—	24	11±0.8	22±1.5	34±2.6	44±2.6	53±3.1	59±2.9	65±2.8	71±3.4
3 mes end arc	30	—	19±1.4	38±1.7	56±1.9	70±1.4	79±1.2	85±1.4	90±1.2	94±1.0
15 mes end arc	—	24	39±4.3	60±5.4	75±5.0	83±4.0	89±3.2	92±2.4	95±1.9	96±1.5

membranous system could continue until the whole dose had left the intestinal preparation. *Hence the differences between the groups must be attributed to such changes in the permeability of the intestinal wall to iodide as were due to the experimental condition.* The iodide loss over the intestinal wall of the primarily intact experimental animal was the standard by which the results of the other experimental groups were judged.

During the 120 minutes that the intestinal preparation was kept *in vitro* its vitality could deteriorate to such an extent that its permeability to iodide was changed. Since, however, the experimental conditions were the same for all the experimental groups, this factor did not affect the results.

Laparotomy performed 30 minutes before the experiment, possibly decreased the passage of iodide through the intestinal wall, and did so definitely when performed 24 hours prior to the experiment. Thus, in some way, the intestinal wall had become *less permeable* to water-soluble iodide. A plausible explanation is that this procedure caused an inflammatory reaction in the peritoneum with the exudation of impervious material on the surface of the intestine. The reaction was able to reach a higher degree of development the longer the period that had elapsed since the operation was performed. There is good reason to assume that the impervious material was fibrin.

When surgically-induced ischemia of the intestinal wall was applied, the permeation of iodide was increased. The increase was already noticeable even when there was only slight ischemia that had been produced shortly before the experiment. This increase was especially pronounced when ischemia was extensive and allowed to continue for 24 hours. The impervious effect which appeared after laparotomy alone, should quite likely occur also after surgically induced ischemia, and then, if anything, be *more pronounced*. In order for surgically induced ischemia to increase the permeation of iodide through the intestinal wall, its damage had to be so pronounced that it could not be compensated by the impermeative effect of the inflammatory reaction. The results also demonstrated that the more extensive the surgically induced ischemia and the longer it was allowed to continue, the greater the increase in the permeability of the intestinal wall to iodide.

These observations, and above all the decrease in permeability to a water-soluble, diffusible substance, which could be established already after laparotomy, made it desirable to investigate whether, under similar conditions, the intestinal wall would allow a *large-molecular* substance to pass through.

Chapter IX. *In Vitro* Experiments with I^{131} Human Serum Albumin (HSA) in the Ischemic Small Intestine

MATERIAL AND METHODS

In the experimental series 152 animals were used. Table IX shows the distribution of the material into experimental groups. In addition to the groups IC, LC-30 minutes and LC-24 hours, a series of groups was included which represented different degrees of surgical ischemia. The effect that this produced after 30 minutes and 24 hours is given. Thus, data are presented on 2 groups representing 3 and 15 mes end arc—30 minutes and on 5 groups representing 3, 7, 11, 13, and 15 mes end arc—24 hours. Table IX shows the number of animals in each group and the mean values for the body weight and for the isolated loop of the small intestine with the standard error.

The method was identical with that applied in the previous section. In this series I^{131} HSA was used (N. V. Philips Duphar, Amsterdam, Holland). The original solution contained 0.2 mCi/ml and was diluted so that at the beginning of the experiment 0.1 ml corresponded approximately to 10 μ Ci. As previously, 0.1 ml was injected into the loop of the small intestine, whose position and size were as defined. The loop had been isolated from the continuity of the small intestine. The radioactive substance was administered after such experimental measures were taken as are indicated by the designation of the experimental groups; these measures have been previously described in detail. The way in which the preparation was kept in a physiologic saline solution, the changing of this environment every 15 minutes, the recording of the radioactivity in this connection, and the calculation of the percentage of the radioactivity that had left the intestinal loop, corresponded in all particulars with what has previously been described.

RESULTS

In Table X the results are given for all the experimental groups and also the periods of time

covered by the experiments. They are expressed as mean values with standard error. They have been plotted against the duration of the experiments in a coordinate system in Fig. 10.

After 120 minutes the IC-group had lost about 50% of the radioactive dose from the intestinal loop. At the outset, elimination was only slight, so that only 15% had escaped after 60 minutes; subsequently, it increased and remained constant for the rest of the experimental period (Table X). About 8% of the dose was then eliminated during each remaining 15-minute period. The course of elimination is shown in Fig. 10.

After 120 minutes the group LC-30 minutes had a corresponding escape of 35%. The latter half of the experimental period accounted for the deviation from the preceding group. During the first 60 minutes elimination of radioactivity from the loop was, on the whole, the same as that in the IC-group. Thereafter it decreased for every new 15-minute period (Table X). The character of the course is presented in Fig. 10.

In the group LC-24 hours the escape from the intestinal loop was substantially less for all recordings. After 120 minutes only 25% of the dose had been eliminated, whereas after 60 minutes the elimination was less than 10% (Table X and Fig. 10).

The groups 3 and 15 mes end arc—30 minutes had practically identical elimination values during the entire experimental period. These amounted to about 30% after 120 minutes. In Fig. 10 the groups have been placed together and the dark shading indicates their joint range area.

Nor did the groups 3, 7, 11, 13, and 15 mes end arc—24 hours show, reciprocally, any significant differences. From Table X it is evident that during 120 minutes the intestinal loop lost about 15–20% of the dose, and after 60 minutes between 5 and 10%. Thus, there was less elimination of radioactivity, at least during the last two 15-minute

TABLE IX. *Characteristics of the material*

Experimental group	Pre-exp. interval		Number of experiments	Weight in g	
	min.	hrs.		Body	Isol. loop
IC	—	—	16	243±8.1	0.7±0.01
LC	30	—	15	223±3.2	0.7±0.03
LC	—	24	15	226±9.2	0.8±0.03
3 mes end arc	30	—	15	211±7.8	0.8±0.03
15 mes end arc	30	—	15	223±9.1	0.8±0.02
3 mes end arc	—	24	15	216±10.5	0.8±0.02
7 mes end arc	—	24	15	201±8.1	0.8±0.02
11 mes and erc	—	24	15	220±6.2	0.8±0.01
13 mes end arc	—	24	15	210±1.4	0.8±0.02
15 mes end arc	—	24	16	212±4.0	0.8±0.02

periods, in these groups than in the corresponding groups with a 30-minute pre-experimental interval. Like the latter, the groups with a 24-hour interval were placed together in a group in Fig. 10, and their range area is indicated by light shading.

The radioactivity which passed through the lumen of the intestinal loop to the surrounding salt solution could have arisen from intact I¹³¹ HSA. If, on the other hand, the albumin had been completely or partly disintegrated, the radioactivity could have represented one or more of its iodized breakdown products or pure iodide.

In order to investigate this question a series of experiments were performed, which have been described in detail elsewhere (Johnson, Nylander & Wikström, 1968). The intestinal loop containing I¹³¹ HSA was placed in a dialysis tube (viscous

cellulose, pore size 24 Å). This thus divided the Krebs–Ringer solution into two compartments, an inner compartment containing the intestinal loop, and an outer compartment which was inaccessible to molecules with larger dimensions than 24 Å. In a parallel experiment with the same incubation time (120 min) the same dose of I¹³¹ HSA was deposited directly into the dialysis tube, i.e. into the inner compartment of the salt solution. In the former case the radioactivity which had left the intestinal loop was distributed equally on both sides of the dialysis membrane. It thus belonged to a molecule which traversed the pores of the membrane, and could not therefore represent intact I¹³¹ HSA. In the latter experiment only about 2% of the radioactivity which was deposited in the dialysis tube was recorded outside the tube, in the outer compartment. The I¹³¹ HSA solution thus contained less than 5% iodized hydrolysate or iodide, which was distributed equally on both sides of the semipermeable membrane.

During different experimental periods when the intestinal loop released significant quantities of radioactivity, the outer salt solution was taken and eluted through a sephadex column (G-200). The distribution of the radioactivity corresponded in all cases, and to a predominant degree, to *iodide*.

DISCUSSION

Thus *in vitro* the mucosa in the diminutive intestinal loop was able during a period of 120 minutes to produce sufficient proteolytic enzyme

TABLE X. *In vitro experiments*

Transmural leakage of radioactivity from the isolated loop under different experimental conditions. The values are given in per cent of the radioactive dose. Mean values with S.E.

Experimental group	Pre-exp. interval		Experimental period in min.							
	min.	hrs	15	30	45	60	75	90	105	120
IC	—	—	3±0.7	5±0.9	9±1.0	15±1.2	23±1.3	31±1.9	39±2.0	47±2.3
LC	30	—	4±0.8	6±0.8	10±1.4	15±2.1	19±3.0	25±3.7	29±4.5	35±5.0
LC	—	24	1±0.4	2±0.4	5±0.7	8±1.4	11±1.8	15±2.6	19±3.5	25±4.9
3 mes end arc	30	—	2±0.5	4±0.8	8±1.4	12±2.1	15±2.8	19±3.7	24±4.5	27±5.0
15 mes end arc	30	—	3±0.6	4±0.7	7±0.8	10±1.1	14±1.7	19±2.6	24±3.0	30±3.6
3 mes end arc	—	24	3±1.1	4±1.0	5±1.1	7±1.3	10±1.8	12±2.1	14±2.6	16±3.1
7 mes end arc	—	24	2±0.7	3±0.7	5±0.5	6±0.6	8±0.7	9±0.9	11±1.5	14±2.2
11 mes end arc	—	24	4±0.9	7±1.3	9±1.4	11±1.7	12±1.8	14±2.3	16±2.4	18±2.9
13 mes end arc	—	24	3±0.9	5±1.5	7±1.7	10±1.9	11±2.0	12±2.3	14±2.4	17±2.6
15 mes end arc	—	24	3±0.6	4±0.9	7±1.2	9±1.6	12±2.4	15±2.6	18±2.9	21±3.3

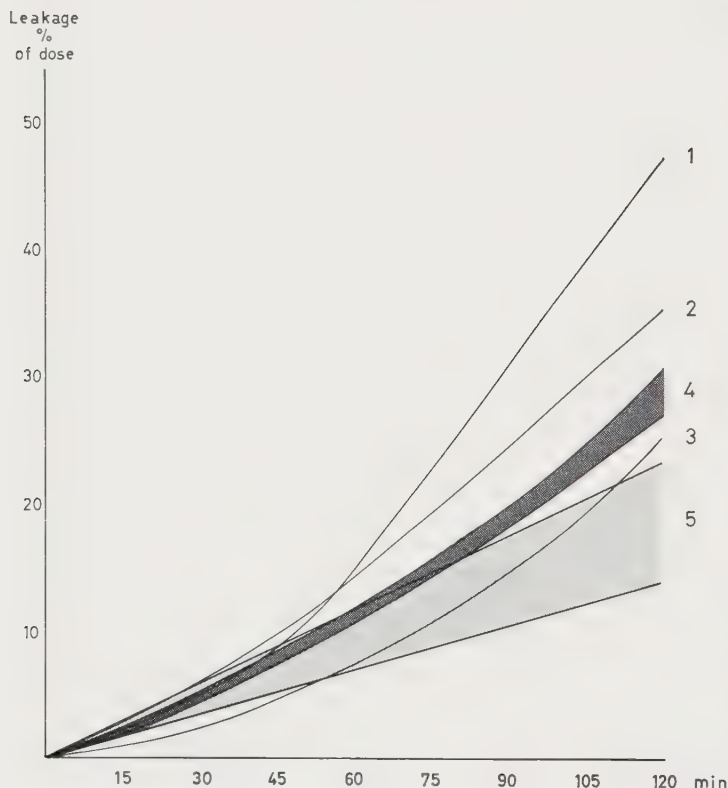


Fig. 10. Disappearance of radioactivity from I^{131} HSA deposited in the surgically ischemic loop kept *in vitro*. Leakage is expressed in per cent of the radioactive dose (vertical axis) plotted against experimental time in minutes (horizontal axis). 1, Experimental group IC; 2, Experimental group LC—30 minutes; 3, Experimental group LC—24 hours; 4, Experimental groups 3–15 mes end arc—30 minutes; 5, Experimental groups 3–15 mes end arc—24 hours. Light shading = range of groups 3–15 mes end arc—24 hours. Dark shading = range of groups 3–15 mes end arc—30 minutes.

to hydrolyze about 50% of the albumin. An expression of the disintegration of the albumin was the radioactivity recorded in the salt compartment. This represented radioactive iodide, which had become separated from the iodized tyrosine of the albumin. The liberated iodide traversed the intestinal wall, according to the existing concentration gradient, to the outer, regularly renewed, salt compartment.

It would have seemed reasonable to assume that there was no—or only minimal—enzymatic activity in the intestinal preparation. The occurrence of radioactivity in the outer salt solution would then have reflected the permeability of the intestinal wall to intact albumin. From the results obtained, the erroneous conclusion could then have been drawn that an intestinal loop from the primarily intact rat allows through a molecule as large as albumin (69,000). Such an apparent leakage was, it is true, only negligible during an initial period (45–60 min) but increased subsequently at a rapid rate. This should indicate an increasing devitalization of the intestinal wall and such a change in its complex membrane system

that such large molecules could pass through relatively unhindered. It was evident from the separation analyses, however, that it was *iodide* that passed through the intestinal wall. The time course of this transit must therefore be given a different interpretation.

It can thus be assumed that the initially slow leakage from the loop represented that time required by the available proteolytic enzymes to exert their effect. After more or less complete hydrolysis of the albumin and liberation of iodide, the iodide leaked out at the rapid rate which was determined by the permeability of the intestinal wall to iodide and the concentration gradient to the outer environment.

On the other hand, the initially negligible passage of iodide through the intestinal wall could be due to the fact that only small amounts of proteolytic enzymes were available in the still biologically intact intestinal loop. After 45–60 min *in vitro* the anoxia could have damaged the epithelial cells so that they disintegrated. Their proteolytic enzymes would be released and the albumin broken down more rapidly. The result

would be that increased amounts of iodide would be released and passed outwards to the salt solution. This latter explanation seems to be the most probable.

The transit of the radioactivity through the wall of the loop in the laparotomized experimental groups was discussed in the foregoing chapter. Even when I^{131} HSA was used, it was *iodide* that left the lumen of the intestine. The theory that the laparotomy procedure reduces the permeability of the intestine to iodide also holds for this experimental series. As in the previous series with radioiodide, the effect was most marked in cases where a longer period had elapsed since the laparotomy. We assume, therefore, that the laparotomy induces an inflammatory reaction in the peritoneum, which, by the deposition of a blocking substance (fibrin) on the serosal surface of the intestine, is able to reduce the permeability of the intestine to iodide.

With regard to the ischemic groups the condi-

tions are rather different. It is evident from the results that in these groups—and to a higher degree the longer the interval between the surgical induction of the ischemia and the experiment—the permeability of the intestinal wall to the liberated radioiodide was reduced. This is in contrast to the results in the pure radio-iodide experiments, where the surgically induced ischemia *increased* the permeability of the wall to iodide, probably as an expression of such devitalization of the membrane complex of the intestinal wall that the reducing effect of the simultaneous inflammatory reaction on the porosity was completely overpassed. In the series with I^{131} HSA the surgical ischemia may have given rise to such damage to the enzyme-producing cells of the mucosa that an important part of the enzyme content was lost before the *in vitro* experiment was set up. It would seem probable that such an effect would be most pronounced when the ischemia has been present for a long period.

Chapter X. Angiographic Investigation

MACROANGIOGRAPHY

Material and Methods

In this experimental series 12 rats were used; they weighed between 210 g and 240 g. The loop of the small intestine, whose position and size has been previously defined, was subjected to ischemia by ligating 3, 5, 7, 11, or 15 mes end arc. For each one of these procedures 2 animals were used. In one of these the loop of the small intestine was also ligated from the intestinal continuity both upward and downward, while avoiding the mesenteric border vessels. The abdominal aorta was exposed immediately below the diaphragm. By means of an indwelling catheter a suspension of barium sulphate (Micropaque-Howards) was infused according to Nylander & Olerud (1960). When, according to the naked eye, the filling of the vessels had been completed, and contrast suspension had emptied itself from the catheterized jugular vein, the intestinal loop was examined, which was situated centrally in the devascularized part of the intestine, with or without isolating ligatures. The results were documented photographically.

Results

In the entire series the ischemic intestinal loop had a cyanotic discoloration, which was most pronounced *centrally* and when a large number of mes end arc were ligated. When 15 mes end arc were ligated this segment was dark reddish blue (Fig. 11).

Moreover, the ischemic loop was tonically contracted. Contraction caused the shortening of the loop and the appearance of contraction rings (Fig. 11).

When the vascular bed of the splanchnic area had been filled with the contrast suspension, the mesenteric end arcades distal to the ligatures, the vasa recta, and the subserosa vessels on the surface of the intestine were also visualized also in the most central part of the ischemic loop. This occurred also when 15 mes end arc were ligated and the intestinal loop was isolated from the in-

testinal continuity by ligatures (Fig. 11). Filling with the contrast medium took place via the proximal and distal anastomoses, which, thus, supplied the area peripheral to the ligated mes end arc and their reciprocal connections.

Discussion

The observed cyanotic change in colour of the loop indicates a dominant *venous* blockade. The condition is well-known clinically (Moore, 1941). The small peripheral veins have no valves, and when arterial pressure is suddenly lowered the blood flows back into the capillary area, which is then filled with venous blood. When the capillaries are subsequently damaged by ischemia, the blood infiltrates the tissue.

Contraction of the ischemic loop should be seen against the background that the smooth muscle layers of the intestine react with spasms when it becomes ischemic (Rives *et al.*, 1948, and Meier & Waibel, 1964). This enduring contraction probably causes further deterioration in the already poor blood flow (Moore, 1941), an assumption that has been experimentally verified by Sidky & Bean (1958).

Macroangiographic visualization of the anastomotic flow to the ligated end arcades, which fills these, the vasa recta, and the mural vessels, shows the capacity of the intestine to withstand extensive surgical ischemia (Glotzer *et al.*, 1962). Even the obstruction of 15 consecutive mes end arc could be compensated for by the anastomotic vessels, and the mesenteric anastomoses alone were sufficient, since the intramural vascular connections of the intestinal loop could be closed by ligatures both upwards and downwards, without the anastomotic flow ceasing.

MICROANGIOGRAPHY (HAEMOGLOBIN STAINING)

Material and Methods

The experiments comprised 14 rats, whose weight was between 215 g and 250 g. As in the previous



Fig. 11. Macroangiography with barium sulphate (Micropaque). The intestinal loop represents maximal devascularization (15 mes end arc). It is closed with two ligatures, which prevent intramural flow. Observe that the

vessels distal to the ligatures and on the intestinal surface have been filled by collaterals. The loop is cyanotically discolored and in a state of contraction.

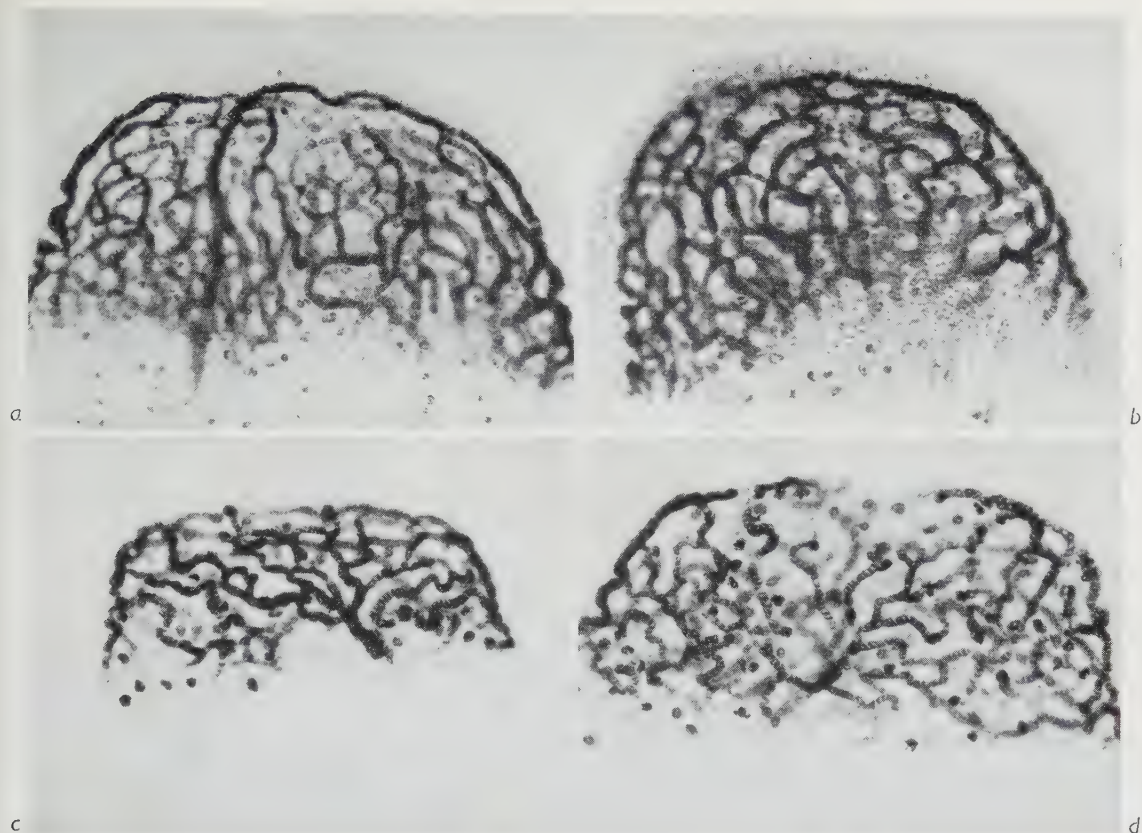


Fig. 12. Microangiography with haemoglobin staining. Villi from the loop in the experimental groups LC (a),

3 mes end arc (b), 5 mes end arc (c), and 7 mes end arc (d).

series, laparotomy was performed and the ligation of 3, 5, 7, 9, 11, 13, or 15 mes end arc. For each of these groups 2 animals were used. In one rat the central loop was isolated from the intestinal continuity by means of ligatures. The abdomen was closed and the animal was kept awake for 30 minutes. On renewed laparotomy the isolated loop or its equivalent was identified and opened longitudinally along the antimesenteric attachment. Microangiography, with haemoglobin staining, was performed on small excised pieces (Nylander & Olerud, 1960).

Results

As Figs. 12 and 13 show, all the vascular components in the villi are filled with blood, even in the groups with pronounced ischemia of the intestine. There was no appreciable difference be-

tween the microangiographic pictures representing different degrees of devascularization.

Discussion

Despite macroangiographic support for the fact that the peripheral vessels are filled via the anastomoses even in the maximally ischemic loop, and that the mesenteric anastomoses alone are sufficient to cope with the circulation when the intramural anastomoses are eliminated, it is nonetheless surprising to find that the capillaries in the villi are completely filled. Entrance to the capillary area is regulated by the precapillary sphincters, which determine the number of functioning exchange vessels (Folkow, 1967); and a large part of the capillary network in the villi can be disconnected by arteriovenous shunting when an intestinal loop is functionally eliminated

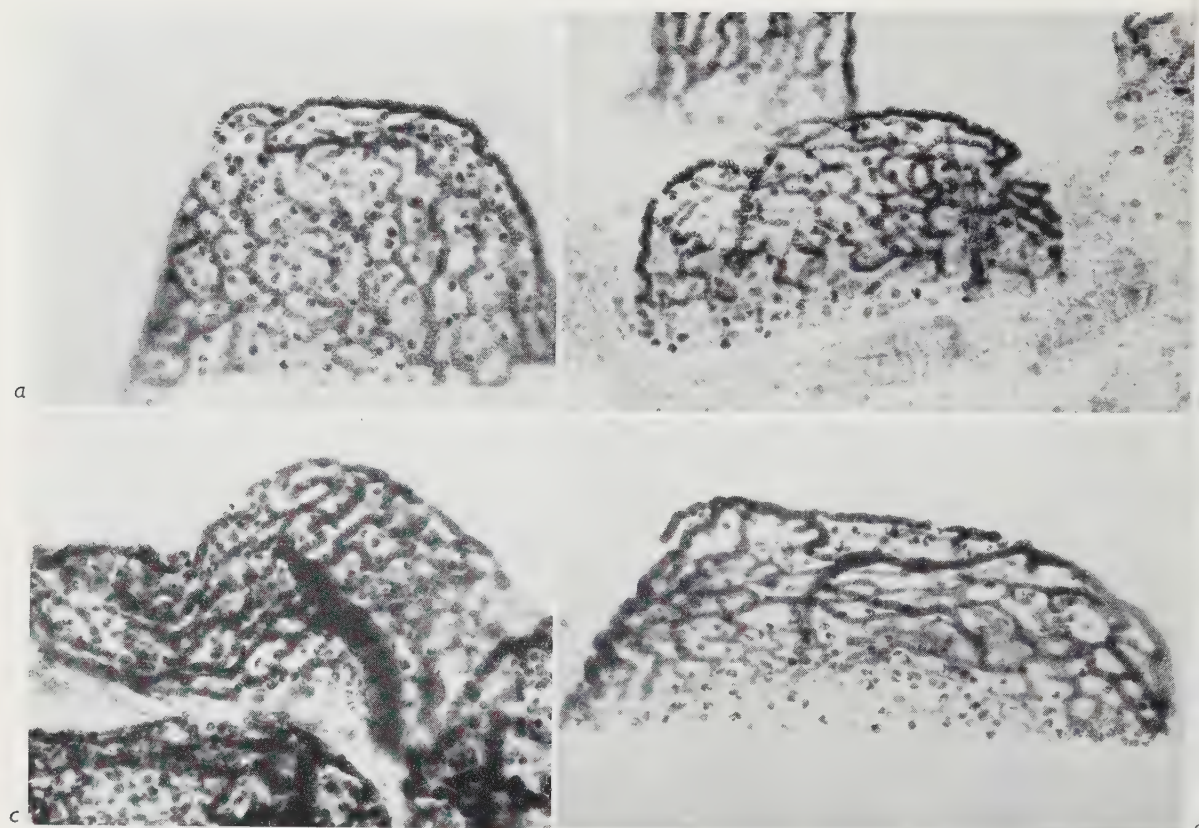


Fig. 13. Microangiography with haemoglobin staining. Villis from the loop in the experimental groups 9 mes end arc (a), 11 mes end arc (b), 13 mes end arc (c) and 15

mes end arc (d). All vascular components, including the capillary network, are filled with blood.

(Nylander & Olerud, 1961). Such extreme ischemia as occurs in this series should, consequently, substantially reduce the filling of the capillaries, which the absorption studies on iodide indicated, since the exchange flow decreased in proportion to the extent of the ischemia. The probable explanation is that the pressure in the anastomoses is not sufficient to withstand the pressure from the venous side, and, therefore, the blood from the veins flows back into the capillaries. These can then be visualized with this technique.

For this reason the investigation was further supplemented.

MICROANGIOGRAPHY (CONTRAST SUSPENSION)

Material and Methods

The material was obtained from the macroangiographic series and the experimental technique was in accordance with that given by Nylander & Olerud (1960).

Results

As is evident from Fig. 14 the central artery in the villus as well as its arcade arterioles and individual capillary loops were filled with the contrast medium when 15 mes end arc were ligated. Several of the capillary loops, however, were filled with blood and prevented the penetration of the contrast medium. In Fig. 14 the left basal vein

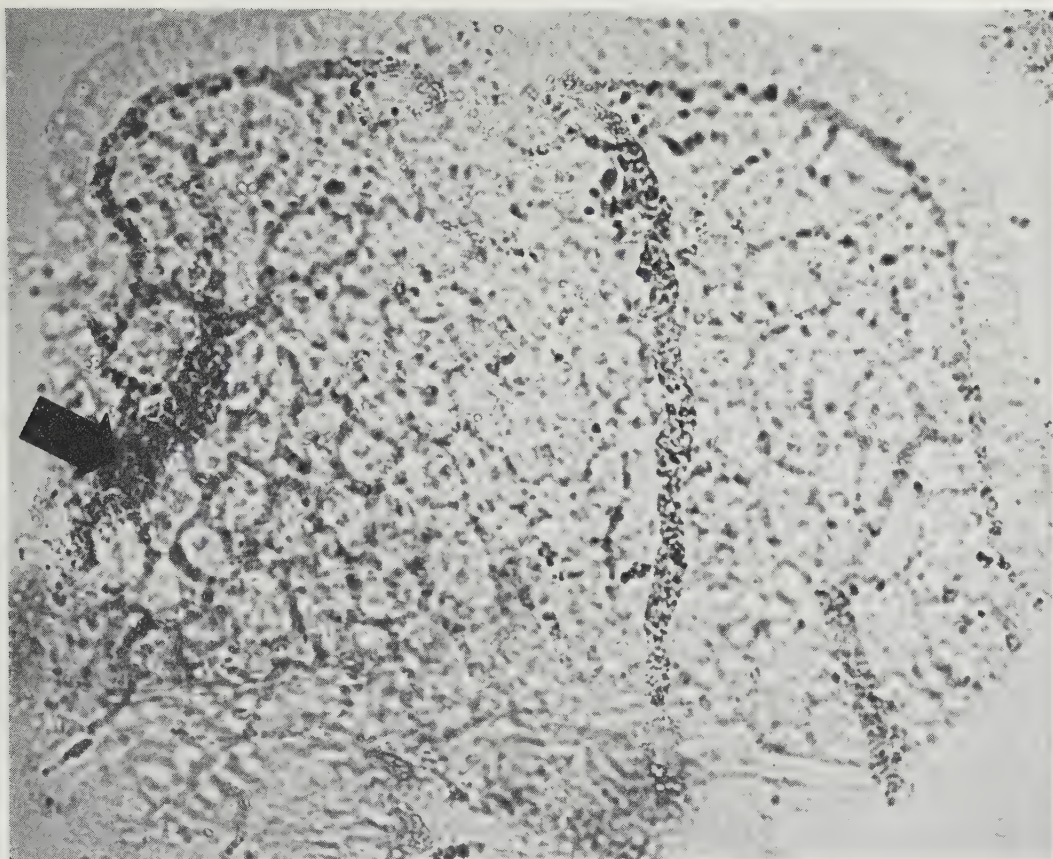


Fig. 14. Microangiography with barium sulphate (Micropaque). Villus from the loop in the experimental group 15 mes end arc. The contrast material from the artery

fills only a small part of the capillary network (right). The rest is filled with blood and so is the draining vein (arrow) which is greatly dilated.

is greatly distended and filled with blood, and this applies also to the adjoining capillary loops. On the other hand, the right basal vein is filled with barium sulphate particles, as are also the adjacent capillaries. The vein is of normal width.

Thus, large parts of the capillary area in the villi of the ischemic loop are not included in the microcirculation, but remain unutilized and filled with blood, which has probably overflowed from the venous system.

Chapter XI. Propulsive Gastrointestinal Motility

MATERIAL

In all, 459 rats are reported on. The material was divided into 5 main groups. The decisive factor was the number of ligated mes end arc. As a control group a series was used in which only laparotomy was performed and the intestinal loop explored which had been made ischemic surgically in the other groups. The group was designated, as previously, LC. The experimental groups, in the strict meaning of the term, with ligation of 7, 9, 11, and 13 mes end arc, respectively, were given the corresponding designations 7, 9 etc. mes end arc.

In addition, a group of intact control animals was used (IC), which was reported on in an earlier methodological study (Derblom, Johansson & Nylander, 1966).

The experimental groups were divided in turn with regard to the duration of the experimental period, which varied from 1 to 4 hours. Thus, the experimental groups consisted of 4 subgroups, with the exception of the LC-group, which was analyzed also after 6 hours. This disposition of the material is shown in Table XI, which also gives the mean body weight with standard error.

METHODS

The propulsive gastrointestinal motility was recorded according to a method previously described by Derblom, Johansson & Nylander, (1963 and 1966). This method has been used in a series of investigations with different experimental variables of surgical interest (Johansson, 1966; Nylander & Wikström, 1967; Nylander, 1967; Johansson & Nylander, 1968, and others). Furthermore, such a mathematical analysis of the results has been developed, that the propulsive activity in particular parts of the small intestine can be compared with that of the small intestine as a whole (Grevsten, Johansson & Nylander, 1967).

Principally, the method records the *net result* of such neuro-muscular activity, in the stomach

and the small intestine, as moves the contents in an aboral direction. Previous methods for these determinations were either not quantitative (conventional roentgenologic technique - fluorocine-matography or abdominal windows respectively) or technically laborious (quantitative chemical analysis of some indifferent reference substance). The technique, which is interesting from other points of view, of recording intraluminal variations in pressure (balloon method, pressure-sensitive transducers, including endo-radiosondes) provides just as little information of this kind as does the principle of recording the electric potentials of the muscular layers of the intestine.

A radioactive substance is used in the present method, which investigates its quantitative distribution in the consecutive parts of the gastrointestinal tract at different times after the substance has been deposited in the stomach. Certain of its properties makes radioactive chromate ($\text{Cr}^{51}\text{O}_4\text{Na}_2$) suitable for this purpose. The substance is not absorbed from any part of the gastrointestinal tract and does not adhere to its mucous membrane, after it has passed an arbitrary section of the intestine. Finally, it does not interfere, in any known way, with the functions of the gastrointestinal tract and possesses suitable radio-physical properties for measurement.

The original radioactive solution was obtained from Institutt for Atomenergi, Kjeller, Oslo, Norway. It was diluted so as to give a specific activity of 100 $\mu\text{Ci/ml}$.

The radioactive chromate was supplied with a test meal with the following composition per deposited dose:

Glucose 1 mg
Phenol red 1 mg
Polyethylene glycol 4000, 5 per cent,
and 10 μCi of $\text{Cr}^{51}\text{O}_4\text{Na}_2$
Phosphate buffer according to Michaelis, pH 7.2
ad 1 ml

The volume of the dose was measured with weighed tuberculin syringes, with calculated reliability of $\pm 5\%$.

TABLE XI. *Body weight in the different experimental groups (g)*

Mean values with S.E.

Exp. period in hours	Experimental group				
	LC	7 mes end arc	9 mes end arc	11 mes end arc	13 mes end arc
1	220±2	214±3	207±4	222±4	229±5
2	249±5	213±3	215±3	228±2	226±5
3	213±3	215±2	217±2	230±4	219±2
4	221±5	255±9	242±8	218±3	232±7

Under brief ether anaesthesia a polyethylene catheter was introduced into the stomach, where the dose was deposited with very slight injection pressure. The rat was awake at the very moment the manipulation was completed. After the given experimental period the animal was killed with ether, the abdomen opened and ligatures made around the cardia and the pylorus. The gastrointestinal tract, comprising the stomach, small intestine and caecum, was dissected out while retaining continuity, and put on a plexiglass plate. The plate, whose length corresponded to that of the specimen (100 cm) was provided with a shallow groove, in which the specimen was extended, with the stomach at one end and the caecum at the other (Fig. 15). With every such maneuver it could be ascertained, through the colour distribution of the indicator in the preparation, that this had not changed. The empty small

intestine of the fasting animal and, at death, its primary contraction, enabled a number of manipulations to be made without its contents being moved.

Recordings were made by passing the stretched gastrointestinal specimen under a scintillation detector, the recording unit of which was connected with an automatic, linear recorder. The transit through the lead container of the scintillation detector was operated by the recorder at a speed synchronous with its own (Fig. 15). In this way a graphic recording was obtained of the quantitative distribution of the radioactive substance in the specimen. That part of the dose which remained in the stomach could readily be identified on the recorded graph. The distance between its distal border (pylorus) and the ileo-caecal angle was divided into 10 consecutive, equal fractions.

The quantitative evaluation was made planimetrically. The parts of the recording corresponding respectively to the stomach and the small intestine fractions were measured individually by planimetry. Finally, planimetry was applied to the whole recording, which corresponded to the total dose. The other values were expressed as percentages of this.

The radioactivity in the stomach and in the small intestine was then measured, each separately, by direct counting. In respect of the stomach, agreement was very good between this and the planimetric method of measurement. Similarly, the primarily measured dose agreed with the sum of the radioactivity recorded in the stomach and the small intestine.

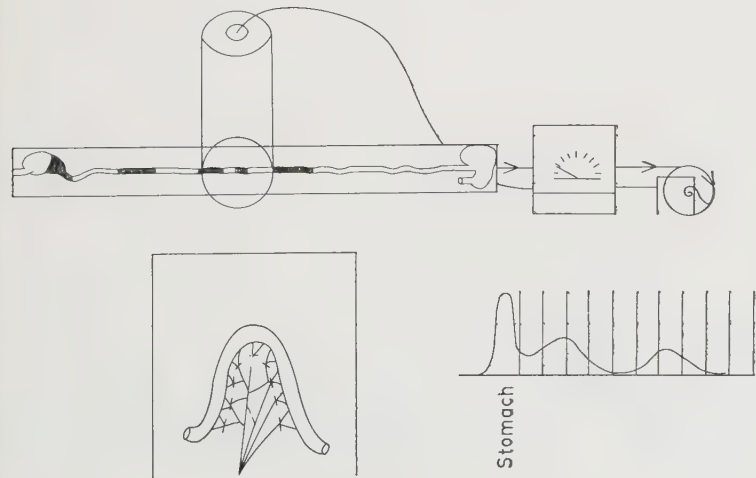


Fig. 15. Schematic representation of recording method for quantitative evaluation of gastrointestinal propulsive motility. The intestinal loop represents an experimental group subjected to surgical ischemia. Automatic recording of radioactivity and graph with characteristic section representing the stomach. This, and the equal-sized, consecutive fractions representing the small intestine are analyzed planimetrically. See text.

TABLE XII. *Weight of stomach in the different experimental groups (g)*

Mean values with S.E.

Exp. period in hours	Experimental group				
	LC	7 mes end arc	9 mes end arc	11 mes end arc	13 mes end arc
1	3.2 ± 0.12	3.1 ± 0.11	3.0 ± 0.13	3.2 ± 0.12	3.3 ± 0.09
2	2.4 ± 0.03	2.4 ± 0.13	2.3 ± 0.12	2.9 ± 0.15	2.9 ± 0.11
3	2.3 ± 0.16	2.2 ± 0.12	2.1 ± 0.11	2.5 ± 0.09	2.5 ± 0.16
4	2.2 ± 0.10	2.5 ± 0.11	2.2 ± 0.10	2.3 ± 0.13	2.1 ± 0.15
6	1.8 ± 0.07				

Discussion

The method has been discussed on previous occasions (see especially Derblom, Johansson & Nylander, 1966, and Grevsten, Johansson & Nylander, 1967). It should be pointed out that it only gives information on the *net effect of the propulsive motility*. On the other hand, it cannot elucidate the separate intestinal motor functions that contribute to produce this result. The tonus and rhythmic contractions of the smooth muscle layers, may, possibly, also contribute towards producing such a net effect, but the main propulsive activity is *peristalsis*. Its principle is correlated with the neuro-muscular structures of the intestine and is independent of nervous influences. The concept net effect comprises, however, also reflexes in the gastrointestinal tract the afferent and efferent paths of which may be both vagal and adrenergic. Hence, what the method records is the sum of *all such motor activity in the intestinal wall as contributes to propel its contents aborally*.

TABLE XIII. *Comparison between the two calculation methods*

DC=direct counting; PA=planimetric analysis. Mean values with S.E.

Exp. period in hours	% of the radioactive dose in the stomach											
	IC				Number of ligated mes end arc							
					7		9		11		13	
	DC	PA	DC	PA	DC	PA	DC	PA	DC	PA	DC	PA
1	20 ± 2	19 ± 2	68 ± 3	66 ± 3	46 ± 5	47 ± 5	52 ± 5	49 ± 4	64 ± 4	65 ± 5	70 ± 3	73 ± 4
2			32 ± 4	35 ± 4	25 ± 4	26 ± 4	40 ± 3	40 ± 4	50 ± 4	51 ± 4	52 ± 4	55 ± 4
3			25 ± 3	25 ± 3	22 ± 3	20 ± 3	31 ± 4	33 ± 5	30 ± 3	32 ± 3	36 ± 5	39 ± 5
4			13 ± 3	15 ± 3	16 ± 3	17 ± 4	21 ± 3	26 ± 4	31 ± 3	34 ± 3	31 ± 4	28 ± 5
6			9 ± 2	10 ± 2								

RESULTS

Gastric Emptying

Weight of stomach

Table XII shows the mean weight of the stomach for all the experimental groups and experimental times. It is evident that the stomach tended to diminish in weight when the experimental periods were prolonged. In the LC-group the organ weight was reduced by approximately 1/3 when the experimental period was prolonged from 1 to 4 hours. The same tendency was observed in all the ischemic groups, where after 1 hour the weight varied between 3.0 and 3.3 g and after 4 hours between 2.1 and 2.5 g.

If, on the other hand, the weights were compared in the different groups for the same experimental period, no tendency was noted at all. Thus, no increase in the weight of the stomach occurred when the ischemia of the intestine was increased.

Discussion. In fasting animals a reduction in the weight of the stomach during the experimental period can give a rough idea of the gastric emptying. At the same time as it empties the comparatively small test meal, secretion, however, is being discharged from its mucous membrane. The amount of this secretion is not known, especially under varying experimental conditions. Consequently, it is not possible by such recording of weight alone, to draw conclusions concerning the emptying of the stomach. The method may possibly be used as a screening test.

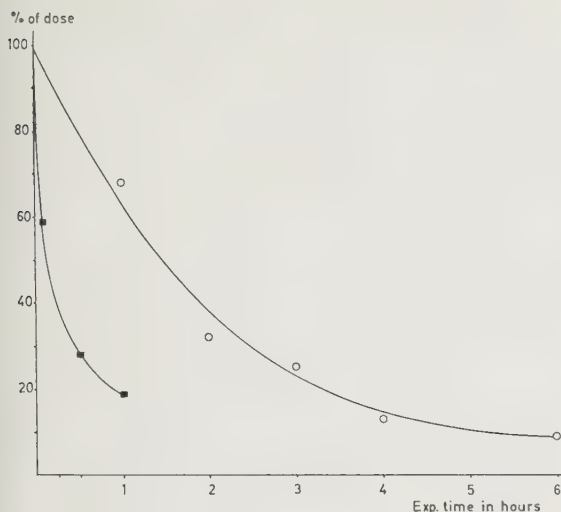


Fig. 16. Course of gastric emptying in the experimental groups (IC black square and LC hollow ring). The radioactivity remaining in the stomach is expressed in per cent of the dose and is plotted on the vertical axis against experimental time on the horizontal axis.

Quantitative analysis with radio-chromate

Table XIII shows the part of the radioactive test dose which was measured in the stomach at the given experimental periods. The results are expressed as percentages of the deposited dose and as mean values with standard error. Both the *direct* recording (direct counting) and the *indirect* estimation (planimetric analysis) are given. The table shows that there is very good agreement between the two methods of calculation.

The course of the gastric emptying is illustrated graphically in Figs. 16-17, where the mean values for direct counting (DC) have been shown at the various experimental periods.

The corresponding values, obtained by planimetric analysis (PA), are also given in the series of tables which show the percentage distribution of the radioactive dose in the gastrointestinal specimen (Tables XV-XX).

In the IC-group, after 5 minutes less than 60% of the dose was found to be present in the stomach. After an experimental period of 15 minutes about 45% were present; after 30 minutes less than 30%, and after 60 minutes less than 20%. The exponential curve in Fig. 16 illustrates the emptying of the stomach in the intact rat, with an initially rapid, and subsequently retarded

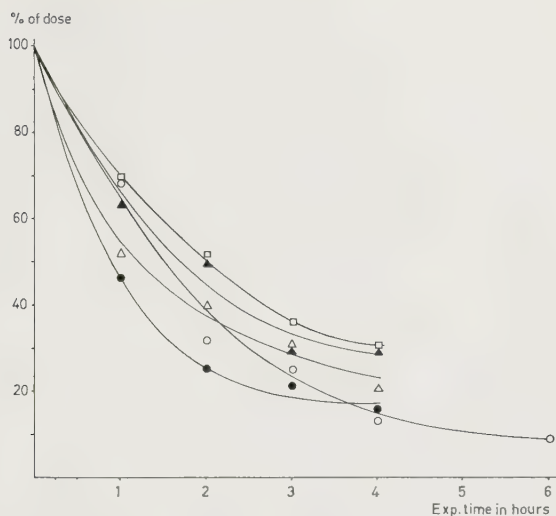


Fig. 17. Course of gastric emptying in the groups LC (hollow ring), 7 mes end arc (black ring), 9 mes end arc (hollow triangle), 11 mes end arc (black triangle), 13 mes end arc (hollow square). The radioactivity remaining in the stomach is expressed in per cent of the dose, and is plotted on the vertical axis against experimental time on the horizontal axis.

course. This material has been previously reported on in detail by Derblom, Johansson & Nylander (1966) and Wikström & Nylander (1967).

After 1 hour the LC-group retained about 70% of the dose in the stomach (Table XIII). The retarded emptying persisted, so that after 2 hours there was still about 35% present in the stomach, and after 3 hours 25%. It was only after 4 and 6 hours that an increasingly small part of the dose was retained in the stomach. When the course of emptying was represented by plotting the values, as a function of the experimental periods, it was found that the characteristic pattern was still retained. This is seen in Fig. 16, where the course of emptying in the IC-group is also plotted.

The group 7 mes end arc retained less than 50% of the dose in the stomach after 1 hour. After 2 hours about 25% were recorded, after 3 hours about 20%, and after 4 hours just over 15% (Table XIII). The course of emptying, as shown in Fig. 17, was still characterized by an initial rapid phase followed by a slower phase. During the former—especially during the first hour—emptying was much more rapid than in the LC-group.

In the group 9 mes end arc after 1 hour the

stomach contained about 50% of the dose and thereafter emptied about 10% every hour (Table XIII). Consequently, after 2 hours 40%, after 3 hours about 30%, and after 4 hours about 20% were recorded. The curve which illustrates the course of emptying had, as is seen in Fig. 17, likewise an initial phase, which, during the first hour, was somewhat more rapid than in the LC-group. Subsequently, the emptying was retarded, so that it corresponded approximately with that of the LC-group.

The emptying of the stomach in the two groups 11 and 13 mes end arc showed close agreement throughout the recordings. Thus, after 1 hour the stomach retained 65–70% of the dose, after 2 hours just over 50%, after 3 hours 30–35%, and after 4 hours about 30% of the radioactive dose (Table XIII). As shown in Fig. 17, in both cases the course of emptying had retained its special character. After 1 hour emptying corresponded substantially to that of the LC-group, but thereafter it was much slower.

Discussion. The effect, on the motility functions of the gastrointestinal tract, which varied surgically-induced ischemia of an intestinal loop may be expected to produce, cannot be determined separately, unless the effect of the laparotomy is first ascertained. This in turn must be evaluated on the basis of the intact experimental animal's situation.

In this investigation the intact control material was not analyzed, but had been on a previous occasion. There is reason to believe that the degree of emptying after 1 hour was somewhat greater than that reported here. A value between 10% and 15% has subsequently been given by Johansson (1966), Johansson & Nylander (1968) and Lindquist (1968).

It has been demonstrated that laparotomy and exploration of the small intestine cause pronounced retardation in the emptying of the stomach. This paralyzing effect can be expressed quantitatively. This is best done by stating the half-time, i.e. the time required to empty half the dose. For the intact, control animals this is about 10 minutes, whereas in the laparotomized animals 90 minutes are required. This effect in *immediate* connection with the operation persists for not less than 3 days, when a moderate degree of retardation is still operative (Nylander & Svensson, 1968).

Despite such pronounced retardation the emptying of the stomach retains much of the character of an exponential function. This pattern of emptying, which has been known since the end of the nineteenth century and, in modern times, is documented for both experimental-animal and clinical material, is, consequently, not affected by laparotomy. Nor do more radical experimental measures, such as vagotomy, resection of small intestine, intestinal obstruction etc., change this principle (Nylander & Wikström, 1967; Nylander, 1967; Nylander & Svensson, 1968). This agrees with the observation made by Thornton *et al.* (1955), that the emptying of the stomach is a very stable function.

We decided to analyze the propulsive gastrointestinal motility in experimental groups where not less than 7 mes end arc had been ligated. Previous absorption studies had shown that only through such extensive devascularization could manifest reduction of the effective exchange circulation of the intestinal mucosa be obtained. However, the expected retardation of gastric emptying in connection with such devascularization did not occur. On the contrary, emptying was *initially more rapid*, so that the half-time was about 60 minutes. The rapid initial phase lasted 2 hours. Even when 9 mes end arc had been ligated the initial, more rapid course of emptying persisted, but was less pronounced and of shorter duration. Only when 11 and 13 mes end arc had been ligated was the effect *inhibitive* in respect of the emptying of the stomach; less during the first hour than subsequently. The half-time in these groups was about 2 hours.

Thus, extensive surgical ischemia of the loop of the small intestine had an *accelerative* effect on the initial period of the emptying of the stomach; an effect which was only eliminated after very extensive devascularization had taken place. The result is both surprising and obscure.

It is considered that motor activity in one part of the gastrointestinal tract can provoke corresponding activity in another part. Relations of this kind have been explained by what are known as long intestinal reflexes (Davenport, 1966). They are regarded as having receptors in the autonomous innervation of the smooth muscle layers of the intestine. When the influence of such a long reflex affects the stomach, it is considered to be invariably *inhibitory* (the ileo-gastric re-

TABLE XIV. Weight of small intestine in the different experimental groups (g)

Mean values with S.E.

Exp. period in hours	Experimental group				
	LC	7 mes end arc	9 mes end arc	11 mes end arc	13 mes end arc
1	10.8±0.28	11.5±0.28	11.3±0.29	12.5±0.27	13.6±0.51
2	12.0±0.30	10.5±0.59	13.0±0.43	14.5±0.49	14.6±0.40
3	8.4±0.50	11.5±0.40	11.7±0.34	13.7±0.41	12.7±0.37
4	8.7±0.14	13.0±0.42	12.7±0.53	13.7±0.34	14.1±0.35
6	8.7±0.18				

flex). In the opposite direction, however, i.e. when increased motor activity occurs primarily in the stomach, the long reflex can transmit such increased activity to a section of the intestine (the gastro-ileal reflex).

In this case the possibility cannot be excluded that a long intestino-gastric reflex is elicited from the ischemic section of the intestine with *accelerating* effect on the emptying of the stomach. The receptors for such a reflex in the smooth muscle layers could be activated by the anoxemia *per se* or its effects on the intestinal wall (oedema, bleeding, congestion, inflammatory reaction etc.) or by the muscular contraction which results from anoxemia (Rives *et al.*, 1948). The effect is reduced and gradually eliminated when extensive devascularization is produced. This is perhaps due to the fact that the receptor mechanism is prevented from functioning on account of increased

anoxemia. Possibly, in this connection, such dilatation of the ischemic section of the intestine may occur as to elicit what is known as an intestino-gastric reflex, with a paralysing effect on the motility of the stomach.

Propulsive Motility of the Small Intestine

Table XIV shows the mean weight of the small intestine for all the experimental groups and experimental times.

The percentage distribution of the radioactive test dose in the consecutive and equal-sized fractions of the small intestine is given in the series of Tables XV–XX. The report covers all the experimental groups in respect of all the experimental periods. The results were obtained by planimetric determination of the graphical recordings, and are presented as mean values with standard error. The corresponding values for the stomach are included. No values less than 5% of the dose are given.

The results were illustrated graphically in histograms. In order to enable a differentiated comparison between the experimental groups the histograms are presented in *two series*. The *first* shows the distribution of the dose in each experimental group at all the experimental times. This form of presentation makes it possible to assess, in each experimental group, the redistribution of the dose as a function of the experimental periods. The *second* form of presentation shows all the experimental groups for one and the same experimental period. In this way, the experimental groups can be compared with one another.

Presentation according to series I

As is shown in Table XVI and Fig. 18, in the LC-group, after 1 hour about 35% of the test

TABLE XV. IC: Percentile distribution of the radioactive dose in the stomach and small intestinal fractions

Mean planimetric values with S.E.

Specimen	Experimental period in min.			
	n=25 5	n=28 15	n=33 30	n=30 60
Stomach	58±3.2	46±3.0	28±2.4	19±2.2
Fraction				
1	9±0.7	5±0.4	4±0.7	3±0.5
2	9±0.6	5±0.5	4±0.4	3±0.5
3	8±0.7	7±0.6	5±0.5	4±0.5
4	7±0.9	10±1.0	8±1.0	7±0.4
5	5±0.7	9±0.7	13±1.1	11±0.5
6		8±1.2	16±1.5	18±1.8
7		5±0.6	11±1.0	17±1.5
8			7±1.1	10±1.2
9				6±0.7
10				

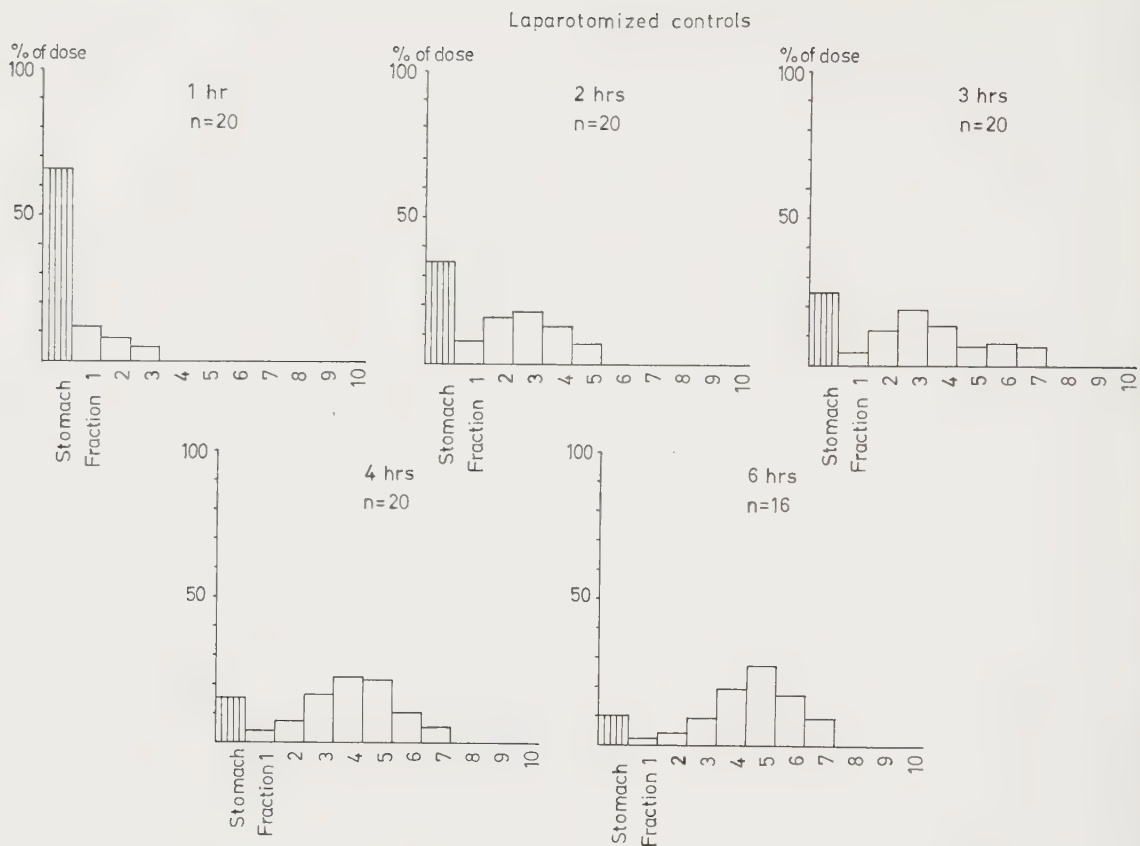


Fig. 18. Presentation according to series I. Histograms representing group LC. The radioactivity is given in per cent of the total dose on the vertical axis; for the sto-

mach, indicated by vertically shaded rectangle, and for the 10 consecutive, equal-sized fractions of the small intestine by unshaded rectangles.

TABLE XVI. LC: Percentile distribution of the radioactive dose in the stomach and small intestinal fractions

Mean planimetric values with S.E.

Specimen	Experimental period in hours				
	n = 20	n = 20	n = 20	n = 20	n = 16
1	2	3	4	6	
Stomach	66±3.3	35±4.1	25±3.4	15±3.1	10±2.0
Fraction					
1	12±1.1	8±1.1	5±0.8	4±0.8	2±0.2
2	8±0.8	16±2.1	12±1.5	7±1.0	4±0.6
3	5±0.9	18±2.2	19±2.8	16±2.8	9±2.1
4		13±2.5	14±1.7	22±2.2	19±2.7
5		7±1.4	7±1.5	21±2.6	27±2.6
6			8±2.6	10±2.1	17±2.5
7			7±3.4	5±2.1	9±1.6
8					
9					
10					

dose had been evacuated into the small intestine. The whole of this portion was found in the three proximal fractions. Fraction 1 was the largest and fraction 3 the smallest.

The 65% that were evacuated after 2 hours were distributed over the proximal half of the small intestine (Table XVI). Fraction 1 had decreased, fractions 2-3 increased, and fractions 4-5 had arisen.

After 3 hours the small intestine had received a further 10%. The greater part was still localized in the proximal half of the small intestine. Fractions 1-2 had decreased somewhat and fraction 3 was dominant. The redistribution in a distal direction that had taken place was mainly manifested in the occurrence of fractions 6-7.

After 4 hours 85% of the dose had entered the intestine. Distribution was still, to the same extent, limited to the proximal half. Within this,

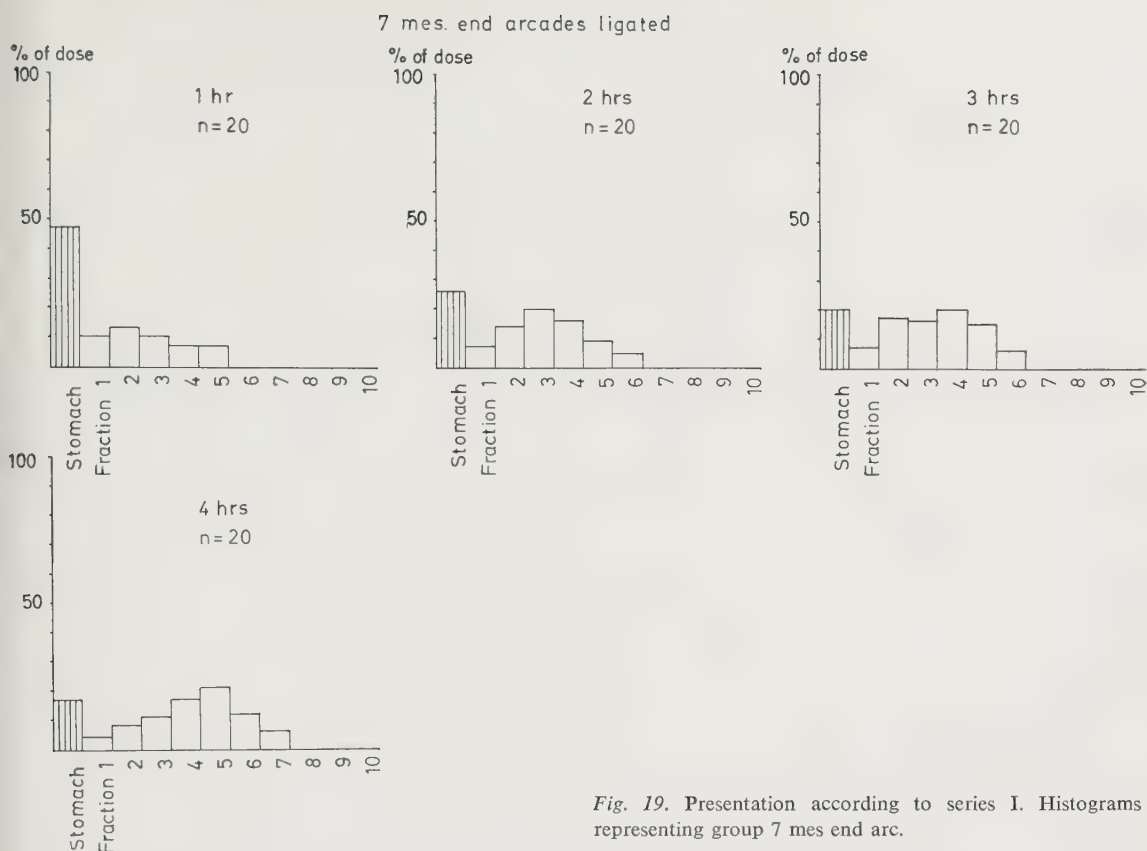


Fig. 19. Presentation according to series I. Histograms representing group 7 mes end arc.

TABLE XVII. 7 mes end arc: Percentile distribution of the radioactive dose in the stomach and small intestinal fractions

Mean planimetric values with S.E.

Specimen	Experimental period in hours			
	n = 20	n = 20	n = 20	n = 20
Stomach	1	2	3	4
Stomach	47 ± 5.2	26 ± 3.9	20 ± 3.4	17 ± 3.8
Fraction				
1	10 ± 1.0	7 ± 1.0	7 ± 1.3	4 ± 0.8
2	13 ± 2.0	14 ± 1.6	17 ± 1.0	8 ± 2.3
3	10 ± 2.1	20 ± 2.3	16 ± 1.9	11 ± 2.3
4	7 ± 1.4	16 ± 2.1	20 ± 2.5	17 ± 2.7
5	7 ± 2.0	9 ± 2.0	15 ± 2.3	21 ± 3.6
6		5 ± 2.2	6 ± 1.3	12 ± 2.9
7				6 ± 2.0
8				
9				
10				

however, a certain degree of distal shift had taken place, owing primarily to the fact that fractions 4-5 had increased and dominated the histogram.

When 6 hours had elapsed 90% of the dose was in the intestine. The continued distal redistribution was characterized by the decrease in fractions 1-3 and the substantial increase in fractions 5-6, so that fraction 5 was the largest.

Group 7 mes end arc. As is evident from Table XVII just over 50% of the radioactive dose had been evacuated into the small intestine in 1 hour. Distribution was limited exclusively to the proximal half of the intestine. All these fractions (1-5) contained approximately equal parts of the dose (Fig. 19).

After 2 hours a further 20% had been evacuated from the stomach and had increased the contents of the small intestine to about 75%. The predominant amount remained in the proximal half. Within this, however, the dose had been redistributed in a distal direction. Table XVII and Fig. 19 show that fractions 3-4 had increased and dominated the histogram. Fraction 6 had come into existence.

When, after 3 hours, the small intestine had

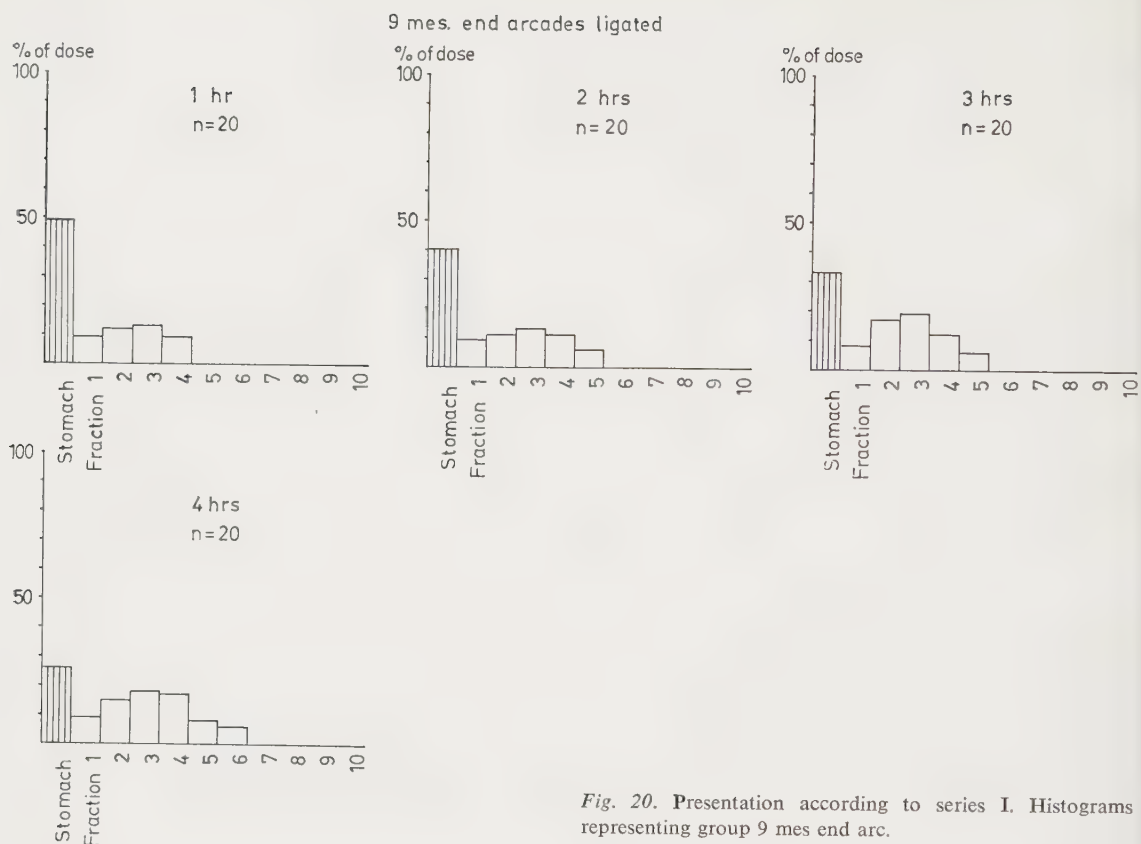


Fig. 20. Presentation according to series I. Histograms representing group 9 mes end arc.

TABLE XVIII. 9 mes end arc: Percentile distribution of the radioactive dose in the stomach and small intestinal fractions

Mean planimetric values with S.E.

Specimen	Experimental period in hours			
	n=20 1	n=20 2	n=20 3	n=20 4
Stomach	49±4.3	40±3.6	33±4.5	26±4.4
Fraction				
1	9±1.0	9±1.6	8±1.3	9±1.8
2	12±1.9	11±1.4	17±2.4	15±2.3
3	13±1.7	13±2.0	19±2.6	18±2.6
4	9±1.6	11±2.1	12±2.6	17±2.4
5		6±1.7	6±1.4	8±1.7
6				6±2.5
7				
8				
9				
10				

received about 80% of the dose, practically the whole portion was still present in its proximal half. Fractions 4-5, had increased, however, as

a result of distal transposition (Table XVII, Fig. 19).

After 4 hours, just over 80% of the dose was in the small intestine and still mostly in its proximal half. However, striking distal redistribution had taken place. The distribution was built up on the dominant fraction 5. Fraction 7 had arisen as the front fraction.

Group 9 mes end arc had, after 1 hour, slightly more than 50% of the dose in the small intestine, and this was exclusively in its 4 proximal fractions, each of which contained about the same amount (Table XVIII and Fig. 20).

After 2 hours, when the intestine had received a further 10%, the evacuated portion was localized in fractions 1-5, of which the last-mentioned had come into existence, whereas the others were for the most part unchanged.

After 3 hours nearly 70% of the dose was present in fractions 1-5. Redistribution had taken place distally, so that fractions 2-3 had increased and were dominant, whereas the others remained almost unchanged.

11 mes. end arcades ligated

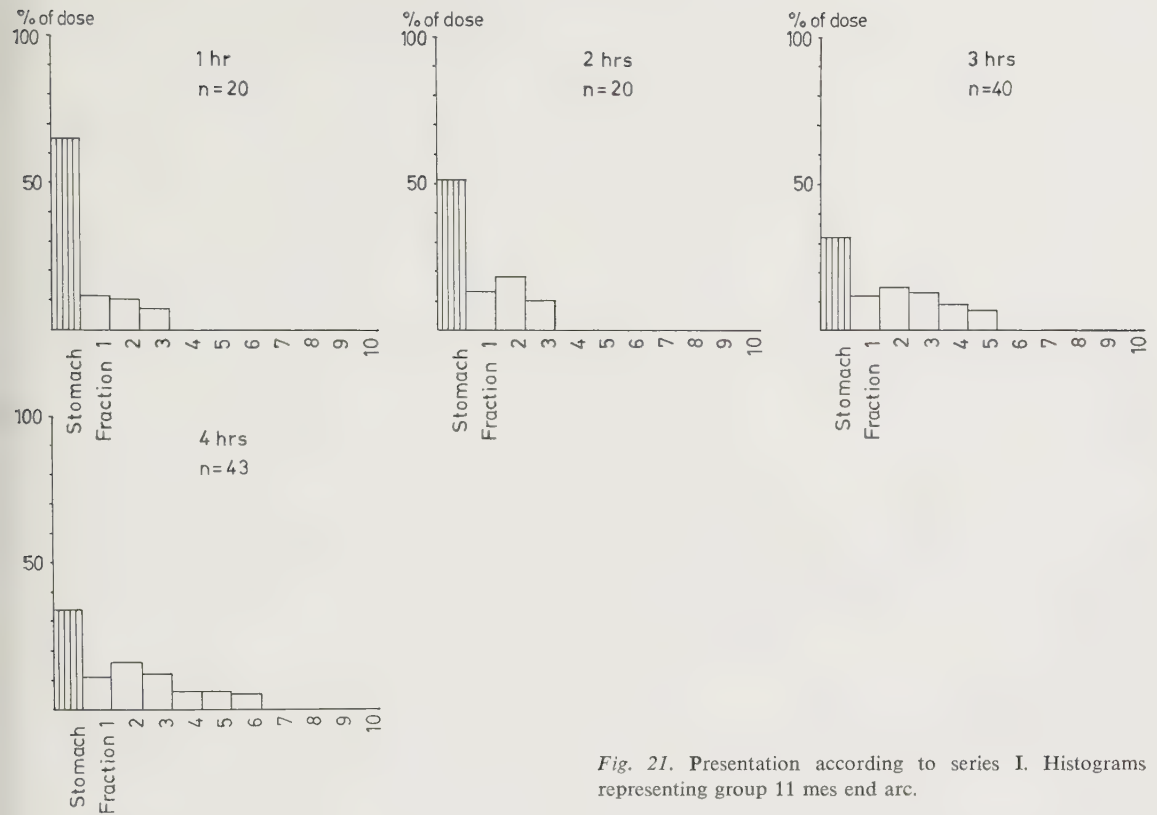


Fig. 21. Presentation according to series I. Histograms representing group 11 mes end arc.

TABLE XIX. 11 mes end arc: Percentile distribution of the radioactive dose in the stomach and small intestinal fractions

Mean planimetric values with S.E.

Specimen	Experimental period in hours			
	n = 20 1	n = 20 2	n = 40 3	n = 43 4
Stomach	65 ± 4.8	51 ± 4.4	32 ± 2.9	34 ± 3.2
Fraction 1	11 ± 1.0	13 ± 1.3	12 ± 1.4	11 ± 1.5
2	10 ± 2.0	18 ± 2.0	15 ± 1.8	16 ± 2.0
3	7 ± 2.0	10 ± 1.9	13 ± 1.5	12 ± 1.8
4			9 ± 1.2	6 ± 1.2
5			7 ± 1.2	6 ± 1.6
6				5 ± 1.5
7				
8				
9				
10				

After 4 hours about 75 % of the dose had been evacuated and was situated in the proximal half. Fraction 6 now formed the front. Fraction 4 had

increased and, together with fraction 3, was the largest.

In group 11 mes end arc, during the first hour 35 % of the dose was evacuated into fractions 1-3 which were about the same size (Table XIX and Fig. 21).

After 2 hours, when about 50 % of the dose had been evacuated, the distribution was still limited to the first three fractions, which had increased. Fraction 2 was the largest.

After 3 hours about 70 % was present in the intestine and fractions 4-5 had come into being.

After 4 hours the intestine had not received any more of the dose, but a further front fraction had arisen. There were no appreciable changes in the other fractions.

In group 13 mes end arc, after 1 hour, about 30 % of the dose was found in the first two fractions of the intestine.

After 2 hours, when slightly more than another 15 % had been evacuated from the stomach, and the intestine contained about 45 % of the dose,

13 mes. end arcades ligated

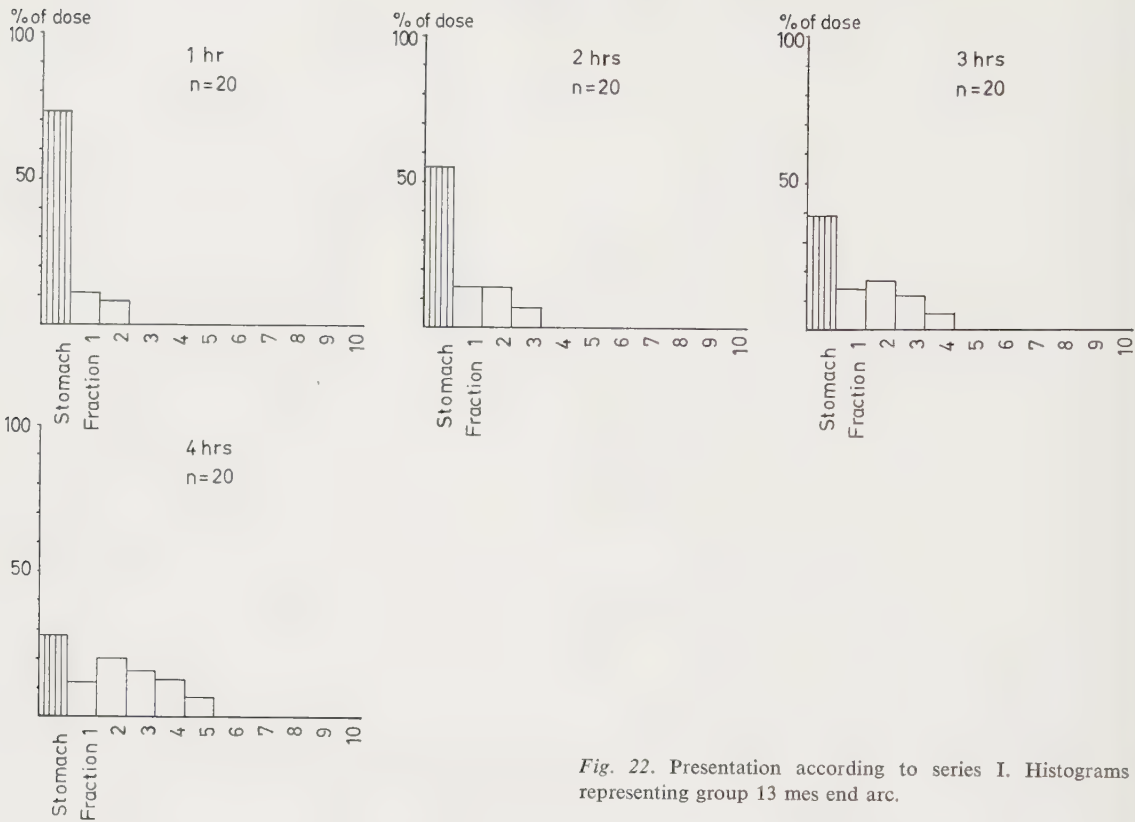


Fig. 22. Presentation according to series I. Histograms representing group 13 mes end arc.

TABLE XX. 13 mes end arc: Percentile distribution of the radioactive dose in the stomach and small intestinal fractions

Mean planimetric values with S.E.

Specimen	Experimental period in hours			
	n=20 1	n=20 2	n=20 3	n=20 4
Stomach	73±3.5	55±4.9	39±4.9	28±5.0
Fraction				
1	11±1.0	14±1.6	14±2.3	12±1.8
2	8±1.5	14±2.4	17±2.8	20±2.9
3		7±1.5	12±2.3	16±2.2
4			6±1.9	13±3.1
5				7±2.0
6				
7				
8				
9				
10				

fraction 3 had arisen as the front fraction. The two proximal fractions had increased somewhat.

Distal redistribution had occurred after 3

hours, when about 15% more had been evacuated into the intestine, which now contained somewhat more than 60% of the dose. Fraction 3 had increased and still another fraction had been added (Table XX and Fig. 22).

After 4 hours slightly more than 70% of the dose was present in the intestine, exclusively in its proximal half. Fraction 5 had arisen as the front fraction, and fraction 4 had increased. The three proximal fractions were essentially unaltered.

Presentation according to series II

Experimental period: 1 hour. When comparing the IC- and LC-groups, as shown in Fig. 23 the difference between both the evacuation of the stomach and the intestinal distribution was striking. In the LC-group only about 35% of the dose had been evacuated into the intestine, when the corresponding figure for the IC-group was slightly more than 80%. In the former group the whole

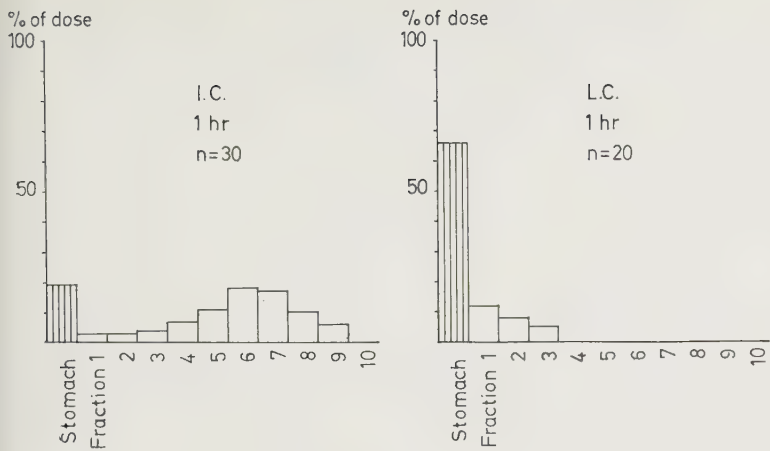


Fig. 23. Presentation according to series II. Comparison between the IC and LC groups. Experimental period 1 hour.

of the evacuated portion was present in fractions 1-3, of which fraction 1 was the largest. In the latter, on the other hand, it was distributed practically over the entire small intestine and mainly in its *distal* half. Fig. 23 shows that fractions 6-7 were dominant and that both the proximal

and the distal fractions were arranged stepwise against these. Fig. 24 shows all the experimental groups and especially the deviations from the LC-group which characterized the groups subjected to surgically-induced ischemia.

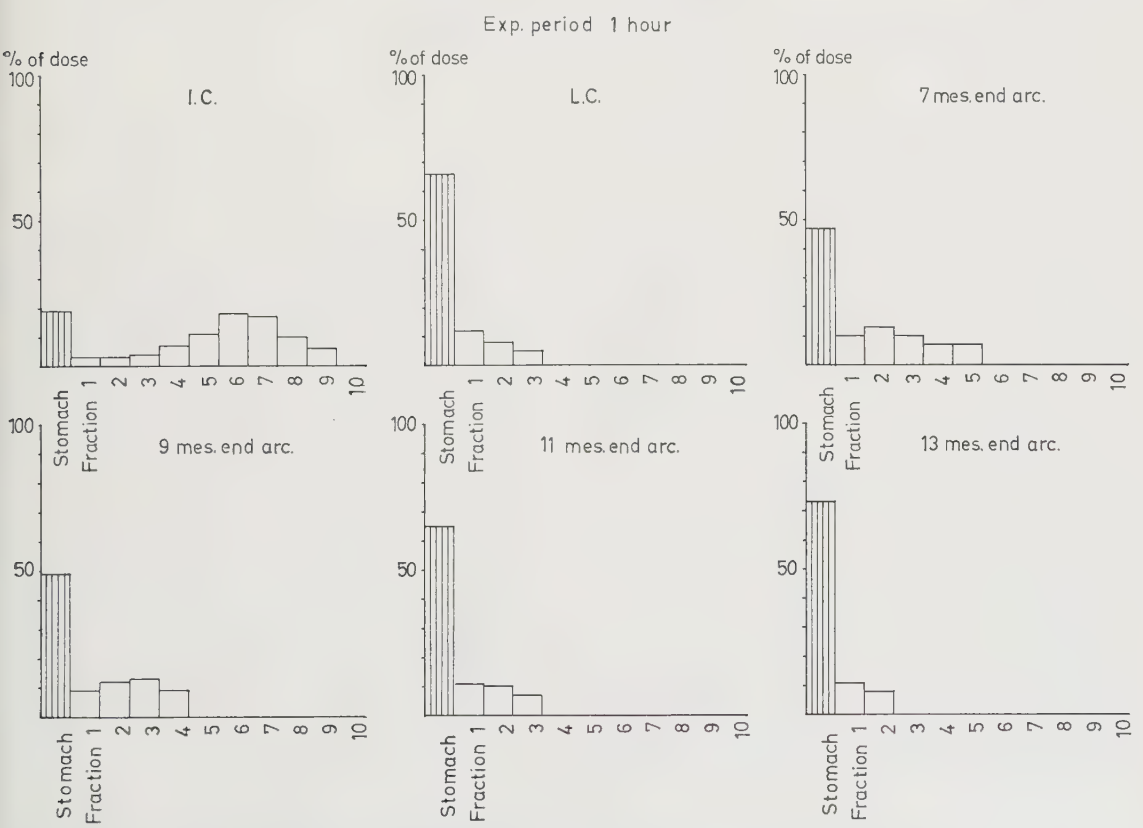


Fig. 24. Presentation according to series II. Histograms representing experimental period 1 hour. The respective experimental group is given.

Exp. period 2 hours

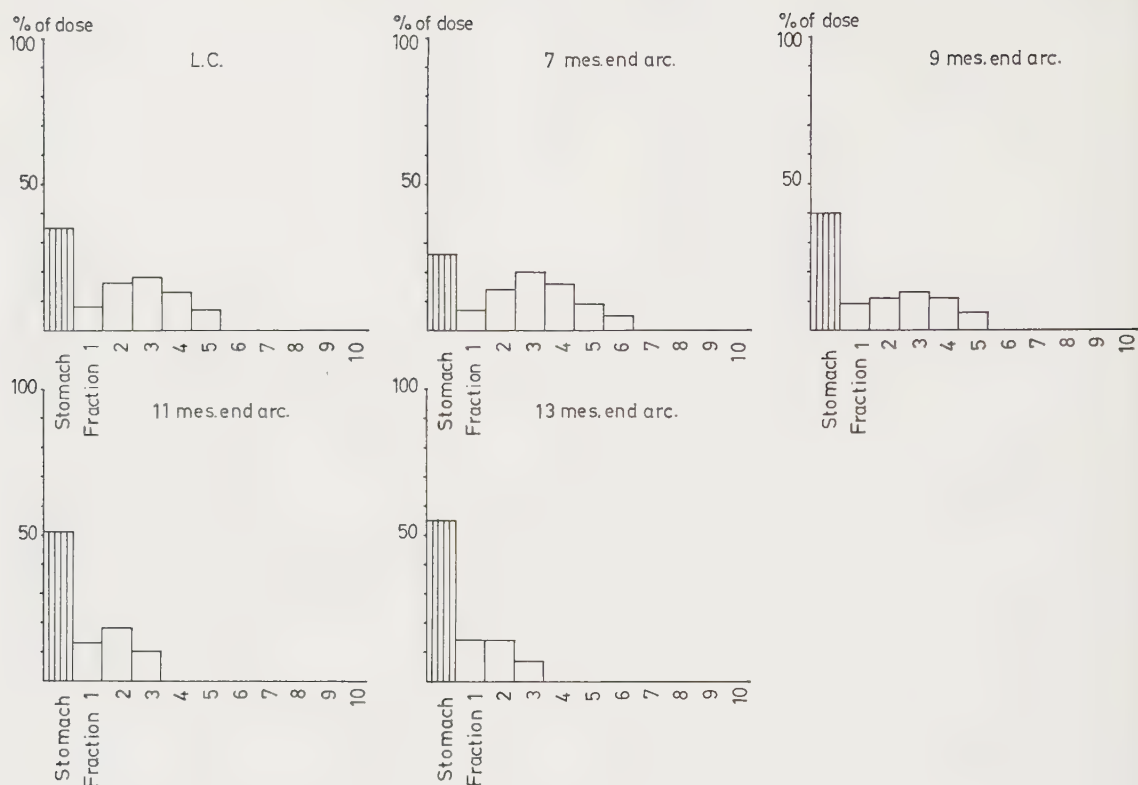


Fig. 25. Presentation according to series II. Histograms representing experimental period 2 hours.

In group 7 mes end arc about 20% more had been evacuated into the intestine, where the distribution was distinctly more distal. In the LC-group fraction 3 formed the front, but in the group 7 mes end arc it was fraction 5. Hence the latter group was more effective with regard to both emptying of the stomach and distal propagation of the evacuated portion.

The group 9 mes end arc had evacuated about the same amount of the dose into the intestine as the preceding group, and thus more than the LC-group, but the distribution was somewhat more proximal, since only fractions 1-4 were involved.

Group 11 mes end arc corresponded to the LC-group with regard to both the emptying of the stomach and propagation into the intestine (fractions 1-3).

In group 13 mes end arc still less had been emptied into the intestine, and had remained there in fractions 1-2.

If the comparisons at 1 hour are coordinated, both the emptying of the stomach and the distal propagation of the intestinal contents were much reduced in the LC-group. Both functions were more effective in group 7 mes end arc, and this applied also to some extent to group 9 mes end arc, whereas group 13 mes end arc was retarded in both these respects.

Experimental period: 2 hours. Fig. 25 shows that in group 7 mes end arc a larger part of the dose was still emptied than in the LC-group, and was then distributed more distally, so that another fraction came into existence (fraction 6).

On the other hand, group 9 mes end arc agreed essentially with the LC-group in respect to the size of the evacuated portion and its distribution in fractions 1-5.

In group 11 mes end arc only 50% of the dose lay in the small intestine. Distribution was confined to fractions 1-3.

Exp. period 3 hours

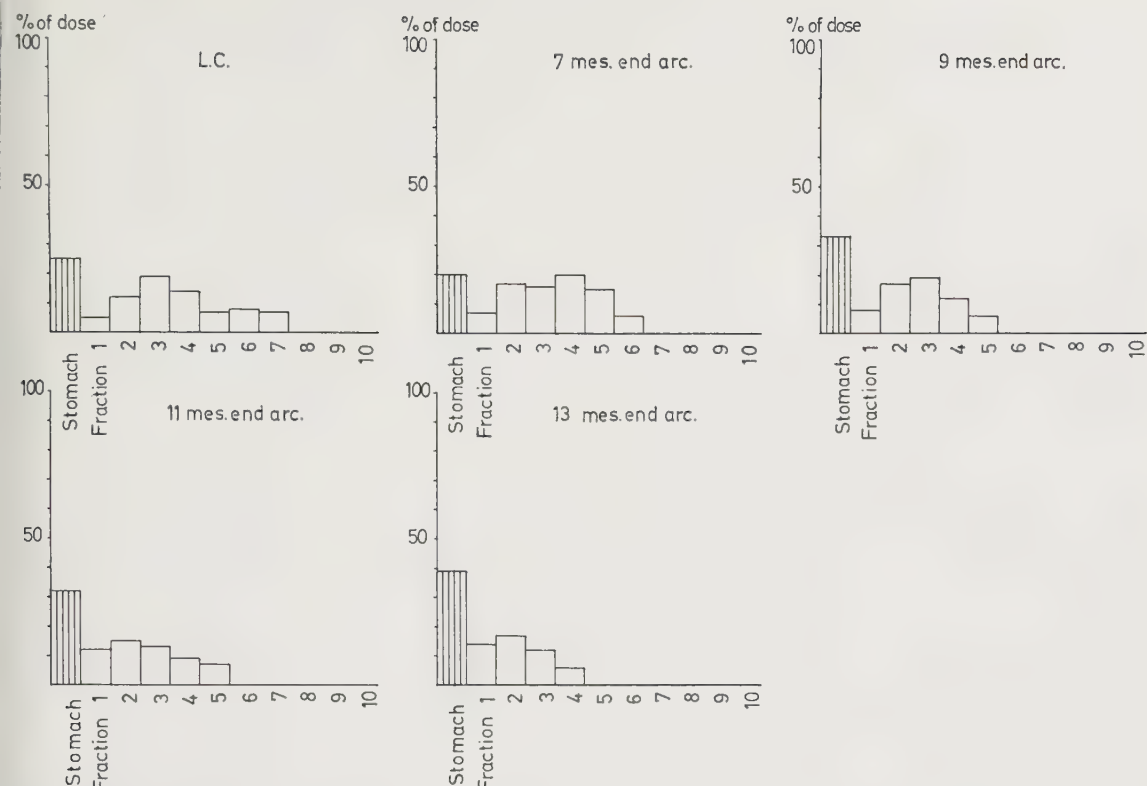


Fig. 26. Presentation according to series II. Histograms representing experimental period 3 hours.

Emptying of the stomach and distal propagation in the intestine were still more retarded in group 13 mes end arc.

After an experimental period of 2 hours a comparison between the groups showed that group 7 mes end arc continued to empty more of the dose into the small intestine than the LC-group did, but the difference was now less; moreover, it distributed its contents in the small intestine somewhat more distally than the LC-group. Whereas, in these respects group 9 mes end arc was approximately equivalent to the LC-group; both the emptying of the stomach and the distal propagation in the intestine were reduced in the groups 11 and 13 mes end arc—more so in the latter group.

Experimental period: 3 hours. Fig. 26 shows that the groups LC and 7 mes end arc had about the same distribution of the dose in the small intestine, although the LC-group had an additional fraction (fraction 7).

Group 9 mes end arc came definitely after the LC-group, with a smaller portion in the intestine and there distributed to fractions 1–5. Even in comparison with group 7 mes end arc it was retarded, with less emptying of the stomach and distal propagation in the intestine.

11 mes end arc showed, on the whole, similar conditions; and in the group 13 mes end arc the tendency was still more pronounced. A smaller portion of the dose was present in the intestine and in fractions 1–4.

A comparison between the groups showed that the LC-group now corresponded essentially to group 7 mes end arc, and that group 9 mes end arc was more retarded. This trend towards retarded emptying of the stomach and propagation in the small intestine was most pronounced in group 13 mes end arc.

Experimental period: 4 hours. There was still manifest agreement between the groups LC and

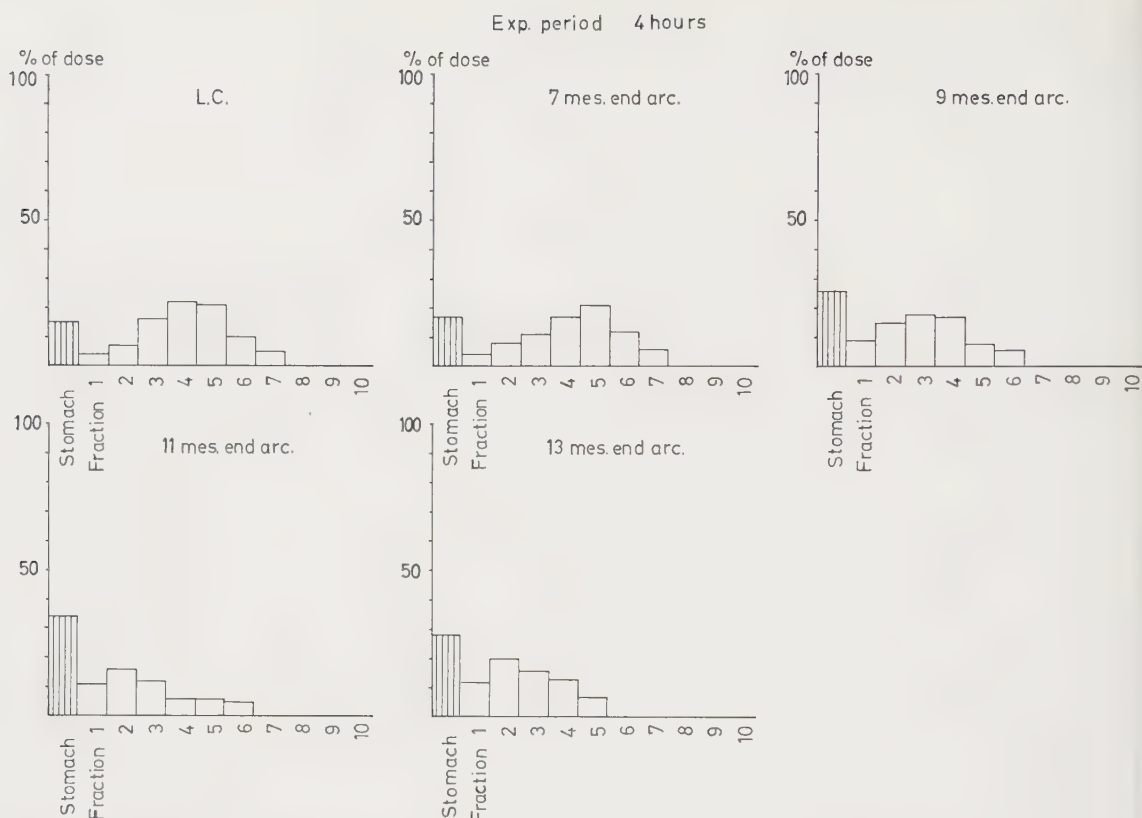


Fig. 27. Presentation according to series II. Histograms representing experimental period 4 hours.

7 mes end arc (Fig. 27). Both the emptying of the stomach and the distribution pattern in the small intestine, where fractions 1–7 were utilized and fractions 4–5 dominated, were similar in the two groups.

In group 9 mes end arc a somewhat smaller portion of the dose was emptied, and was distributed proximally in the intestine, a condition which, via group 11 mes end arc, was most pronounced in group 13 mes end arc. In the latter case only fractions 1–5 were covered by the test dose.

Comparisons showed that groups LC and 7 mes end arc agreed with each other, but starting from 9 mes end arc the small intestine received a smaller portion of the dose, and its distribution was increasingly proximal.

Discussion

The retarded emptying of the stomach after laparotomy thus results in an extremely slow propagation of the evacuated portion in the small intestine. Only after 4 hours was a distal distri-

bution pattern obtained that corresponded to that which the intact control animals presented already after 1 hour. In principle, this effect is well-known from clinical activities, but has not been previously expressed quantitatively.

The stomach had an *initial* period of motor passivity when only an insignificant portion of the test meal was emptied into the intestine. When it recovered its motor activity, the propulsive motility of the intestine dealt with the contents and distributed them more and more distally. Thus, the amount emptied from the stomach seemed to determine, in every situation, the quantitative distribution pattern of the substance in the intestine. Provided the intestine obtained sufficient material, it seemed to have the autonomous capacity of propelling this a considerable distance. This conception is supported by the distribution picture of the laparotomized animals after 4 hours, when the stomach had emptied a large portion of its contents and had distributed them in the small intestine in a way which was characteristic of a

corresponding degree of evacuation in the intact control animals. Thus, with regard to the laparotomized animals, there is probably support for the hypothesis, that the emptying mechanism of the stomach was decisive for the recorded effectiveness of the propulsive motor activity of the intestine. The relation between these two functions has been previously documented in intact control animals by Grevsten, Johansson & Nylander (1967). The correlative condition applied to the comparatively early stages of the course, when the proximal 2/5 of the small intestine were active and the rest passive. Subsequently, when also the distal small intestine obtained propulsive effectiveness, the test substance was propagated to the colon.

The experimental groups with different degrees of localized, intestinal ischemia must be judged against the background of the above data. When the standardized ischemia was least pronounced in the intestinal loop (7 mes end arc), the emptying of the stomach was, as previously pointed out, more effective, at least during the first hour, than in the laparotomized controls. This surprising condition gave rise to the consequent larger, evacuated portion being distributed, in a corresponding degree, quantitatively more *distally* in the intestine. The same tendency, though much less pronounced, was observed when local ischemia was increased (9 mes end arc). Only on very pronounced devascularization (11 mes end arc), when the amount emptied by the stomach after 1 hour corresponded with that of the laparotomized control animals, was the intestinal distribution of the dose quantitatively identical for the groups. Finally, the extreme group (13 mes end arc), which initially had the most pronounced retention in the stomach, had also the insignificant, evacuated portion distributed most proximally in the intestine. Subsequently, in all the experimental groups and for all the experimental periods, the initial passivity of the stomach gradually decreased, and a larger amount of the dose was delivered to the intestine. In all the cases the distal distribution of the intestinal contents seemed quantitatively to be dependent upon the extent to which the stomach was emptied. Even in these experimental groups, with experimentally produced circulatory disturbances in a restricted intestinal loop, a correlation was suggested between the quantitative emptying capacity of the

stomach and the propagation of the evacuated portion in the proximal parts of the small intestine. The larger the part of the dose evacuated the more it was distributed over a larger area of the small intestine.

The reason why a comparatively moderate ischemia in a loop of the small intestine caused both more effective emptying of the stomach and distal propagation of the intestinal contents is obscure. When the more rapid emptying of the stomach was discussed in the preceding section it was suggested that there might be a long reflex between the ischemic loop of the small intestine and the stomach. It was assumed that in this way, moderate intestinal ischemia could cause accelerated emptying of the stomach.

On the basis of this discussion, the more effective distal distribution, in the intestine, of the evacuated portion of the dose, was regarded as a direct consequence of the reflex-induced, increased emptying of the stomach.

When the local intestinal ischemia was accentuated, the effect, however, was the contrary, i.e. the emptying of the stomach was retarded, a smaller portion of the dose reached the intestine and was subjected to only insignificant propagation in a distal direction. It might then be supposed that the receptor mechanism for the presumptive long intestinal reflex had been lost. Alternatively, it might be supposed that ischemia of this degree of severity had, instead, caused such an intestino-gastric reflex that motor activity of the stomach was paralyzed.

Finally, the operation inducing ischemia might be conceived of as causing such damage that local propulsive paresis occurred in this special section of the intestine. This could affect the proximal section of the intestine in such a way that it could not utilize its propulsive capacity. Since, however, as has been previously stated, a certain correspondence exists between the amount emptied by the stomach and the distal propagation in the small intestine, such a reaction in a proximal direction could also affect the stomach.

The results obtained did not conclusively shed light on any of the theories advanced. In order to assess the propulsive effectiveness in individual sections of the intestine in relation to the degree of emptying of the stomach, such mathematical analyses of the results, as could afford further information, were indicated.

Chapter XII. Mathematical Analysis of the Quantitative Distribution of the Test Dose in the Small Intestine

In collaboration with S. Grevsten

BASIC PRINCIPLES

The expressions for the propulsive motility of the small intestine reported on in the preceding chapter can, as previously shown by Grevsten, Johansson & Nylander (1967), be analyzed by a special ratio method:

$$\mu_i = \frac{x_i}{V + \sum_{j=1}^{i-1} x_j},$$

where

μ_i = the ratio for the fraction i (the designation fraction is used in the sense previously defined),

x_i = the percentage portion of the radioactive dose in fraction i ,

V = the percentage portion of the radioactive dose in the stomach,

$\sum_{j=1}^{i-1} x_j$ = percentage portion of the radioactive dose in all the fractions proximal to the given fraction i ,

The mathematical function for the small intestine's propagation of its contents is put, in accordance with this analytical method, in relation to the corresponding function for the emptying of the stomach. It is assumed that the latter has, under normal conditions, an exponential character. If, in such a weighting both functions are identical, μ_i will be constant for all fractions of the small intestine. If, on the other hand, the function for the intestinal propulsion does *not* follow the emptying of the stomach, μ_i cannot be constant. The incongruent relation between the functions will then be decisive for how μ_i varies. Non-constant μ_i implies, in other words, considerable difficulties in interpreting the ratios of the motility functions. Good guidance, with regard to the approximate interplay between the functions, can be obtained from an *intact normal material*. Propagation by the small intestine under

normal conditions and for different times after the radioactive substance has been administered to the animals, will, in what follows, form the basis for the assessment of such deviations as are caused by the experimental measures.

RESULTS AND CONCLUSIONS

For all the experimental groups and experimental periods μ_i -values in the fractions of the small intestine are given which contain not less than 5% of the total dose (Tables XXI-XXVI). The corresponding values are illustrated graphically in Figs. 28-33. The results are commented on for every experimental group, the report on which is introduced by the relevant table of results and corresponding graphical illustration.

IC-group (Table XXI and Fig. 28). This series has been analyzed previously (Grevsten, Johansson & Nylander). After 5 minutes the distal front of the test dose had reached fraction 5, and after 15 minutes fraction 7. For both these experimental periods μ_i was constant in all the fractions (mean = 0.12). When the experimental periods were prolonged to 30 and 60 minutes respectively, the μ_i -values rose to a maximum in fraction 6. This peak was interpreted as an expression of propulsive passivity in the intestine distal to fraction 6. The corresponding analysis of another group of intact animals gave results which, in principle, were entirely in agreement with those reported above (Grevsten, Johansson & Nylander).

LC-group (Table XXII and Fig. 29). When interpreting the μ_i -values in this experimental group the following assumptions were made. The emptying of the stomach and the propulsive motility of the small intestine follow the same exponential course as under normal conditions. On the basis of the results obtained in the IC-group it could then be assumed that μ_i had a mean

TABLE XXI. Quotient values (μ_i) for IC

Experimental period in min.	Small intestinal fraction									
	1	2	3	4	5	6	7	8	9	10
5	0.15	0.13	0.11	0.08	0.06					
15	0.11	0.10	0.13	0.16	0.12	0.10	0.06			
30	0.14	0.13	0.14	0.20	0.27	0.26	0.14	0.08		
60	0.16	0.14	0.16	0.24	0.31	0.38	0.26	0.12	0.07	

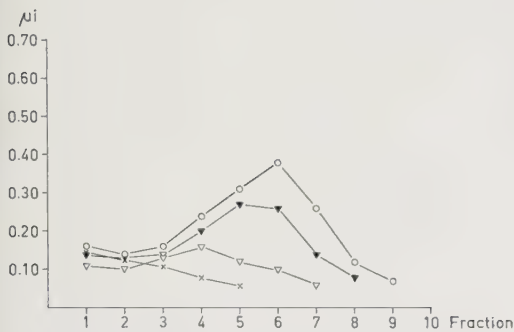


Fig. 28. Graphic representation of the ratio values (μ_i) for the consecutive, equal-sized fractions of the small intestine. Group IC. $\times$, Experimental period 5 min; ∇ , Experimental period 15 min; $\blacktriangledown$, Experimental period 30 min; $\circ$, Experimental period 60 min.

value of 0.13 ± 0.02 (standard deviation for variable ratios).

There are reasons for assuming that the stomach was either entirely passive or had begun a very slow emptying and regained its normal function only at a late stage. After 1 hour the μ_i -value for fraction 1 = 0.18, and for fraction 2 = 0.10. Thus, an accumulation of the dose had already occurred in fraction 1, and distal to this the intestine could be supposed to be propulsively passive. Such a conception was supported by the insignificant emptying of the stomach after 1 hour and by the very proximal distribution of the eva-

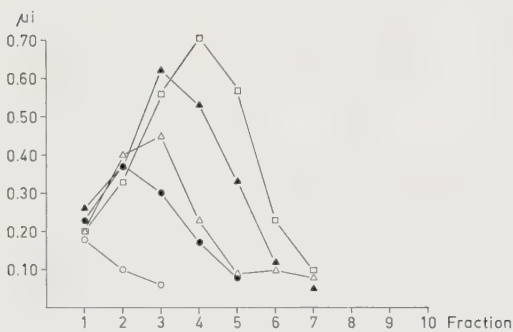


Fig. 29. Graphic representation of ratio values (μ_i). Group LC. $\circ$, Experimental period 1 hr; $\bullet$, Experimental period 2 hrs; $\triangle$, Experimental period 3 hrs; $\blacktriangle$, Experimental period 4 hrs; $\square$, Experimental period 6 hrs.

uated portion in the small intestine. The distal front of the dose was thus represented by fraction 3, whereas in the IC-group, after the same period, it had reached fraction 9.

After 2 hours the μ_i -values formed a distinct peak in fraction 2. The μ_i -value in fraction 1 was also higher than the relevant values in the IC-group. Such an accumulation of the dose in fraction 2 was likewise interpreted as implying that the small intestine lacked propulsive effectiveness distal to this level. After 3, 4, and 6 hours the maximum of the μ_i -values gradually assumed a more distal position (the highest μ_i -value after

TABLE XXII. Quotient values (μ_i) for LC

Experimental period in hours	Small intestinal fraction									
	1	2	3	4	5	6	7	8	9	10
1	0.18	0.10	0.06							
2	0.23	0.37	0.30	0.17	0.08					
3	0.20	0.40	0.45	0.23	0.09	0.10	0.08			
4	0.26	0.37	0.62	0.53	0.33	0.12	0.05			
6	0.20	0.33	0.56	0.71	0.57	0.23	0.10			

TABLE XXIII. Quotient values (μ_i) for 7 mes end arc

Experimental period in hours	Small intestinal fraction									
	1	2	3	4	5	6	7	8	9	10
1	0.21	0.23	0.14	0.09	0.08					
2	0.27	0.42	0.43	0.24	0.11	0.05				
3	0.35	0.63	0.36	0.33	0.19	0.06				
4	0.24	0.38	0.38	0.42	0.37	0.15	0.07			

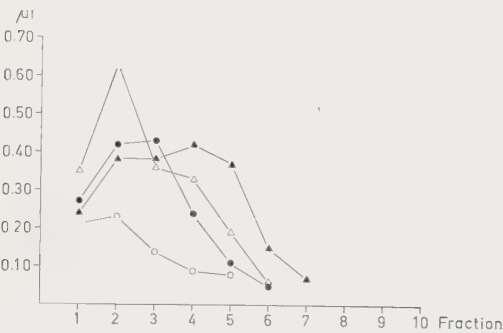


Fig. 30. Graphic representation of ratio values (μ_i). Group 7 mes end arc. $\circ$, Experimental period 1 hr; $\bullet$, Experimental period 2 hrs; $\triangle$, Experimental period 3 hrs; $\blacktriangle$, Experimental period 4 hrs.

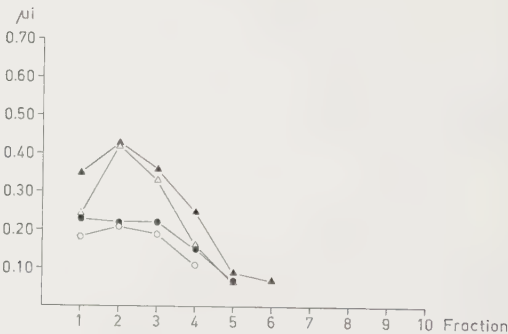


Fig. 31. Graphic representation of ratio values (μ_i). Group 9 mes end arc. Symbols, see Fig. 30.

3 hours was represented by fractions 2-3, after 4 hours by fraction 3, and after 6 hours by fraction 4). This might indicate that the intestine gradually recovered its propulsive function proximally and in a distal direction. Thus, after 6 hours it had regained its normal function both in the stomach and in fractions 1-4. In other words, the small intestine recovered its function more slowly than the stomach; this was manifested in the μ_i -peaks, which, in this group, even after 6 hours were more proximal than after 1 hour in the IC-group.

Assessments of the μ_i -values in the actual experimental groups are based in the following on the values of the LC-group.

Groups 7 and 9 mes end arc (Tables XXIII-XXIV and Figs. 30-31). On comparison with the LC-group μ_i -values diverged especially when the experimental period was 1 hour. The groups 7 and 9 mes end arc had, in fractions 2-3, μ_i -values around 0.20, whereas the corresponding values in the LC-group were approximately 0.15. Moreover, the distal front of the dose had reached fractions 5 and 4, while in the LC-group it had remained in fraction 3.

Alternative 1

The relevant divergences between the groups could be random. They might be due to the difficulty in dealing, with sufficient precision, with

TABLE XXIV. Quotient values (μ_i) for 9 mes end arc

Experimental period in hours	Small intestinal fraction									
	1	2	3	4	5	6	7	8	9	10
1	0.18	0.21	0.19	0.11						
2	0.23	0.22	0.22	0.15	0.07					
3	0.24	0.42	0.33	0.16	0.07					
4	0.35	0.43	0.36	0.25	0.09	0.07				

the time factor. On account of the exponential character of the functions, the course was much more rapid during the first hour than subsequently. The hypothesis that such divergences were due to chance, gained further support from the observation that they did not occur between the LC-group and groups 11 and 13 mes end arc, respectively.

If, however, the differences in the μ_i -levels were real, this could imply that the emptying of the stomach was more rapid during the first hour in the ischemic groups than in the LC-group. That is to say, the stomach had recovered its function at an earlier stage, and/or with greater effectiveness than after only laparotomy. The high μ_i -value in fraction 2 for both the ischemic groups might indicate that at this stage, the small intestine had not recovered to the same extent, and that the propulsive effectiveness of the stomach was greater. Such a conclusion, however, required further substantiation. If the stomach was initially emptied more rapidly in the experimental group subjected to ischemia, this should have persisted during the period that the small intestine recovered its activity proximally and in a distal direction (see LC-group above). Such a recovery of the propulsive activity of the intestine should have resulted in a peak μ_i -value distal in the intestine in the experiments that had continued for the longest time (3-4 hours). This condition, which was observed in the intact control animals, should have occurred simultaneously with a peak in fractions 1-3, on account of an accumulation due to the fact that the emptying function of the stomach was more rapid than the propagation in the intestine. However, no such double peak was observed.

Alternative 2

The following data can be taken as supporting the view that the divergences in question in the μ_i -values and the front propagation were not of a random nature.

Both the experimental groups 7 and 9 mes end arc, which had been subjected to ischemia, manifested the same type of divergences from the LC-group (μ_i -values and propagation front).

From earlier sections it is known that in the LC-group, during 1 hour, only about 30% of the dose was evacuated into the intestine, where its distal front reached fraction 3. In both these re-

spects the LC-group corresponded to the conditions in the extreme groups subjected to ischemia, 11 and 13 mes end arc. When surgical ischemia was more moderate in groups 7 and 9 mes end arc, the stomach had emptied just over 50% of the dose, the distal front of which was situated in fractions 5 and 4 respectively.

The double peak for the μ_i -values, which was said to be required under *alternative 1*, may be without relevance; since in *no* experimental group had the distal front of the dose reached so low a position in the intestine that such a peak had time to develop as was observed in the intact controls already after 30-60 minutes.

A comparison between the group 7 mes end arc and the LC-group when the experimental period was 2 hours showed μ_i -values in the latter that formed a peak in fraction 2 ($\mu_i=0.37$), and in the former a rather more prominent peak in fraction 3 ($\mu_i=0.45$). The fronts of the polygons were represented by fractions 5 and 6, respectively. When the experimental period was prolonged the peak was displaced in group 7 mes end arc distally in the intestine, approximately after the same pattern as in the LC-group.

On the other hand, group 9 mes end arc retained its peak in fraction 2 throughout all the experimental periods and, in this respect, differed from both LC and 7 mes end arc. If the distal propagation front of the dose was compared in the same way, it agreed in 7 mes end arc with that of the LC-group, i.e. it was represented by fractions 6-7; whereas in group 9 mes end arc, it was retired to fractions 5-6. For such longer experimental periods (3-4 hours) the emptying of the stomach in group 7 mes end arc and in the LC-group was likewise nearly identical; but in 9 mes end arc the effect was definitely less effective (see earlier sections).

In short, groups 7 and 9 mes end arc showed, after an experimental period of 1 hour, great similarities, which in turn diverged from the corresponding characteristics in the LC-group. In accordance with the discussion in *alternative 1* and *alternative 2*, the analysis was interpreted as indicating that, in these groups subjected to moderate ischemia, initially the function of gastric emptying was accelerated. Whether this was due to an earlier recovery of a function primarily absent, or that the motor effectiveness, which was in progress the whole time, was initially better,

TABLE XXV. Quotient values (μ_i) for 11 mes end arc

Experimental period in hours	Small intestinal fraction									
	1	2	3	4	5	6	7	8	9	10
1	0.17	0.13	0.08							
2	0.26	0.28	0.12							
3	0.38	0.34	0.22	0.13	0.09					
4	0.32	0.36	0.20	0.08	0.08	0.06				

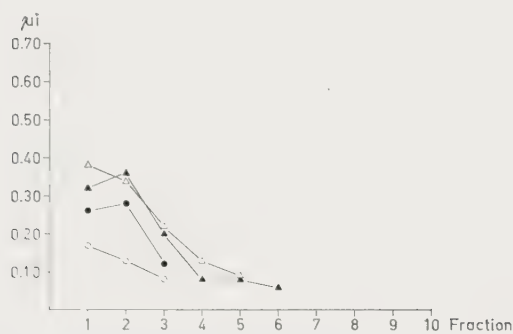


Fig. 32. Graphic representation of ratio values (μ_i). Group 11 mes end arc. Symbols, see Fig. 30.

could not be determined with certainty. This primarily more effective function of the stomach possibly did not have a similarly effective counterpart in the propulsive activity of the intestine. When the experimental period was prolonged, the differences between the groups 7 mes end arc and LC were equalized; whereas group 9 mes end arc did not show a proximal recovery of intestinal propulsion with distal continuation. Previous analyses of the degree of emptying of the stomach and the distance propagated in the small intestine agreed with these conclusions.

Groups 11 and 13 mes end arc (Tables XXV–XXVI and Figs. 32–33. Since these ischemic groups showed pronounced similarities with regard

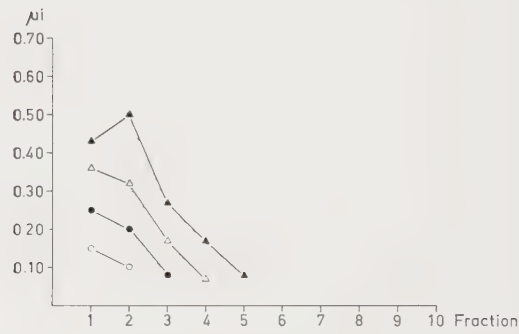


Fig. 33. Graphic representation of ratio values (μ_i). Group 13 mes end arc. Symbols, see Fig. 30.

to μ_i they are assessed together. After 1 hour the μ_i -values were of an ordinary order of magnitude in fractions 1 and 2 (μ_i 0.13 ± 0.02), indicating an ordinary stomach-emptying function, i.e. this function agreed with the propagational function of the intestine. As was pointed out previously, both the emptying of the stomach and the propagation of the dose in the small intestine were greatly reduced, but, apparently, to the same extent. The distal front of the dose was situated, in group 11 mes end arc, in fraction 3, and in 13 mes end arc, in fraction 2. When the experimental periods were prolonged (2, 3, and 4 hours respectively) the μ_i -values were increasingly higher in fraction 1, and successively lower in the distally situated fractions. A distinct accumu-

TABLE XXVI. Quotient values (μ_i) for 13 mes end arc

Experimental period in hours	Small intestinal fraction									
	1	2	3	4	5	6	7	8	9	10
1	0.15	0.10								
2	0.25	0.20	0.08							
3	0.36	0.32	0.17	0.07						
4	0.43	0.50	0.27	0.17	0.08					

lation of the dose occurred already in fraction 1, indicating that distally the small intestine was propulsively passive. If a propulsive function existed and continued, and the experimental period was further prolonged, still another peak could be expected to appear distally. Such a slow propagational function should exert an effect down to fraction 6 and there cause further accumulation (see previous analysis of the IC-group). When such extensive surgically-induced ischemia of the intestine had been performed as in the groups 11 and 13 mes end arc, the intestine apparently lost motor propagation capacity and did not recover it during the experimental periods covered by this investigation.

DISCUSSION

This analytical technique was used previously to demonstrate that normal emptying of the stomach and propagation in the small intestine are, from a mathematical point of view, identical functions in the initial stage of the distal propagation of a test substance. Subsequently, this relationship held good only for the proximal 3/5 of the small intestine, whereas its remaining portion was regarded as passive from the point of view of propulsion. Here, propulsive activity only set in later, when the contents were fed into the colon, according to a linear function (Johansson & Nylander, 1968).

The analyses reported on showed that this normal condition was appreciably distorted by laparotomy alone. This operation caused pronounced inhibition of both the emptying of the stomach and the propulsive activity of the small intestine. The retardation of the functions was most marked initially and recovery was late. This occurred more rapidly in respect to the stomach, so that accumulation took place high up in the small intestine. Gradually, the small intestine also recovered its propulsive function, but even after 6 hours it did not cover more than 2/5 of the intestine, and in the distal part motor activity was absent.

When comparatively moderate ischemia was surgically induced in a loop of the small intestine, this caused, in comparison with the laparotomized control animals, an initially *accelerated* emptying of the stomach. To a certain extent this had its

counterpart in the proximal fifth part of the small intestine. The initial acceleration of both the emptying of the stomach and the proximal propulsive activity in the intestine decreased at an early stage, however, and the functional pattern came essentially to correspond with that of the laparotomized control animals.

When very extensive, surgically-induced ischemia was performed, both the emptying function of the stomach and the propulsive motility of the intestine were strongly inhibited. The latter function was most affected, and there was greater difficulty in its recovery.

In the earlier discussion, it was suggested that the extent to which the small intestine received an adequate content from the stomach also determined its ability to gradually propagate this effectively. In other words, the order of magnitude of the emptying of the stomach was decisive for the way in which the evacuated portion was distributed in the intestine. The greater the emptying of the stomach the further distally was the centre of the quantitative distribution of the evacuated portion. The analysis made has modified somewhat this conception; and has made it seem probable that the emptying of the stomach is severely affected by laparotomy and by intestinal ischemia; but, that, as a rule, the propagational function of the small intestine is affected still more severely. Above all, it takes longer to recover. The intimate congruence, which was previously thought to exist, between the emptying of the stomach and the propulsive function of the small intestine can thus be disturbed by the experimental measures of this study.

Chapter XIII. General Discussion

There is reason to believe that many diseases with symptoms from the abdominal organs have *vascular* causes. Such an assumption gains special support from the increased arteriosclerotic morbidity with its suspected relation to increased length of life, motor inactivity, luxury consumption, obesity etc. The often disastrous, acute occlusion of the main trunks of the mesenteric vessels is, thus, not the only expression of occlusive vascular disease in the abdomen. Long before the final occlusion, a condition of vascular insufficiency may find clinical expression. There is also much to indicate that changes in the peripheral mesenteric vessels and/or intramural vessels can cause abdominal symptoms where, among other things, or, perhaps, above all, intestinal paralysis is a main feature.

This investigation aims at dealing with a special aspect of this problem, namely, whether ischemia in a loop of the small intestine can affect the propulsive motility in the entire gastrointestinal tract. This question has never been previously elucidated experimentally.

In order to study such a relation it is necessary that the degree of ischemia can be varied in a reproducible way, and that the propulsive motility of the gastrointestinal tract can be determined quantitatively. First the possibilities will be discussed of obtaining differentiated and standardized ischemia in a loop of the small intestine.

The vascular arrangement of the small intestine is such, that interruption of the blood flow is often ineffective on account of the abundance of anastomosing vessels. In order to obtain significant degrees of regional ischemia, very peripheral obliteration of the mesenteric vessels is required. In other words, it is necessary to ligate the vascular ramifications immediately connected with the mesenteric attachment. In the rat these ramifications connect adjacent secondary vascular arcs and are here called *mesenteric end arcades* (mes end arc). If a consecutive number of these are ligated, the possibility of anastomotic flow will be least *centrally* in the devascularized part

of the intestine, where, therefore, the maximal effect of the procedure should be evaluated.

In order, as far as possible, to produce ischemia in the same part of the intestine, devascularization was always begun at a constant distance from the ileo-caecal angle. This distance was also defined with its number of mes end arc.

The method of ligating the mesenteric vessels connected with an intestinal loop of *given length* may seem simpler and more reliable. When increased ischemia is required the devascularized part of the intestine is lengthened. In the same way a constant distance can be measured from the ileo-caecal angle. The length of the small intestine, however, is subjected to wide variations, since the condition of its tonus changes; especially when ischemic, it is strongly contracted (Rives *et al.*, 1948). Attempts to apply this principle did not yield reproducible results when the circulation was assessed by the elimination of radio-iodide from a central loop.

However, the method of ligating a consecutive number of mes end arc could not be accepted as quantitative merely on an anatomical basis. It was considered necessary to have a more precise conception of the degree of ischemia. The quantitative recording of blood flow in the intestinal wall is difficult. The methods are technically intricate and, in certain respects, uncertain. A survey was made by Folkow, 1967, whose group (Folkow *et al.*, 1963) developed a refined technique for the continuous recording, regionally in the intestine, of pressure, flow, capillary filtration capacity etc. Such determinations are laborious and require long-standing familiarity with the technique, and are, for different reasons, too highly specialized for this purpose. Furthermore, they are performed with the peritoneal cavity open which would have been a definite drawback in this investigation.

The elimination by diffusion of radio-iodide from an intestinal loop of constant length is an *indirect* measure of the exchange circulation in its mucous membrane. It must then be made cer-

tain that the animals are identical from the point of view of iodide metabolism, and that the iodide concentration of the tracer solution is constant, factors which together constitute the concentration gradient over the barriers between the intestinal lumen and the capillary blood. Since, moreover, the available mucosal surface is kept constant, its exchange circulation is the only variable between the experimental groups. The absorption of radio-iodide from such a standardized loop was demonstrated to be a good indicator of the extent of the ischemia. Only when 7 consecutive mes end arc had been ligated was the ischemia so pronounced that passive absorption of radio-iodide was significantly retarded.

In the experiments made to ascertain the gastrointestinal propulsive motility this was taken into account, and the degree of surgical ischemia was varied between the ligation of 7 and 13 mes end arc; and the material was divided into experimental groups according to the number of ligated mes end arc.

In an earlier work (Derblom, Johansson & Nylander, 1963) a special form of recording was introduced, what is known as the *tail curve*. It represented a continuous recording of radio-iodide appearing in the rat's tail (extravascular space) after the radioactive tracer—as in these experimental series—had been deposited in an isolated intestinal loop. In these experiments the inclination of the tail curve had a very high correlation with the elimination of radio-iodide from the intestinal loop and was thus a simple method for evaluating indirectly the exchange circulation in the loop.

In situations where very extensive devascularization had been performed there was reason to suspect that the ischemic intestinal wall had been damaged to such an extent that the radio-iodide leaked out and was absorbed from the peritoneum. This leakage could be defined as insignificant by a special experimental model, what is known as the "*double-rat*" experiment. The intestinal loop with the radio-iodide was put, during the experiment, into the peritoneal cavity of another rat, from which the transmural leakage of iodide was absorbed and made available for recording. The experimental model proved to be very useful and can be applied to other experimental situations where it is desired to ascertain

how a transient change in environment can influence the functions of the intestine.

In a series of *in vitro* experiments when the isolated intestinal loop was kept for long periods in a physiologic saline environment, its permeability to radio-iodide was evaluated. When the animal had been previously laparotomized the intestinal wall became more impermeable, which decreased the passage of radio-iodide. This effect of laparotomy has not been previously described. This, and to a still greater extent, the ischemic operations on the intestine, should cause an inflammatory reaction in the peritoneum. The exudative phase should bring about, among other things, fibrin precipitation on the intestinal surface, which, in this respect, should affect the permeability.

Ischemia produces, however, such pronounced damage to the intestinal wall that the permeability to iodide *increases* above the normal, despite the considerable reducing effect on the porosity which is probably provoked by the inflammatory reaction.

In the experiments with I^{131} HSA the proteolytic enzymes of the intestinal loop disintegrated the iodinated albumin so that only *iodide* passed outwards through the intestinal wall. This substance could not, therefore, be used for studying the permeability of the intestinal wall to albumin. Instead, it was found that variations in this enzyme activity, together with the permeability of the intestine to iodide, and the concentration gradient to the salt environment, determined the iodide transit through the wall. The ischemic cell damage probably empties a large proportion of the enzyme content of the epithelial cells, so that *in vitro* the loop cannot disintegrate the iodinated albumin to a normal extent.

The ischemic loop had the macroscopic appearance of *venous* circulatory insufficiency, with the cyanotic colour well-known in clinical experience of mesenteric vascular occlusion. The picture has been explained by the flowing back of venous blood into the capillary area when arterial pressure is lowered (Moore, 1941).

When representative parts of this material were subjected to angiography, it was found that even the most pronounced form of the induced ischemia was incapable of preventing the anastomotic flow from filling the vessels distal to the ligatures and on the surface of the intestine. Microangio-

graphy showed that the contrast suspension had gained access to all the villi and there had filled parts of their capillary bed. The rest of the capillaries and, above all, the greatly dilated veins were, on the other hand, filled with blood. Thus the microangiographic picture seemed to be in agreement with Moore's conception, arrived at theoretically, that under these conditions the venous blood flows back into the capillary area.

The extent to which the propulsive motility of the gastrointestinal tract was influenced by the quantitatively well-defined stages of surgical ischemia was determined by a method that proved suitable and reliable for this range of application. This, and the mathematical method of analysis, used for the evaluation of the results, have been discussed in detail previously (Derblom, Johansson & Nylander, 1966). The method records what is termed the propulsive net effect, the result of such intestinal motor functions as propel the contents in an aboral direction. And, what is a distinct advantage, it also makes possible the simultaneous recording of gastric emptying and propulsive intestinal activity. By means of the mathematical analysis, the differentiated propulsive motility, in various parts of the small intestine, can be expressed so as to provide information on the relation between this motility and the function of gastric emptying.

In this way it was possible to express the relations between propulsive motility of the gastrointestinal tract and regional ischemia in the small intestine.

The effect of regional ischemia cannot be evaluated, however, unless it is projected free from the additional influence of the necessary laparotomy.

It was found that laparotomy alone produced substantial retardation of gastric emptying and, in principle, a similar slowing down of propagation in the small intestine. With regard to the stomach it was not possible, on the basis of this information, to determine whether emptying was totally absent during an initial period and, subsequently, re-established, or, if it was active to a slight extent from the outset and then increased. The very small amount evacuated was distributed within an extremely restricted proximal part of the small intestine. When the experimental time was prolonged the emptying of the stomach was increased and also the evacuated

portion appearing distally in the small intestine. Only after 4-6 hours, however, did these conditions approximate to what the gastrointestinal tract of the intact rat was able to produce after 1 hour.

When the ischemia induced was *moderate*, more rapid emptying of the stomach developed and the intestine propagated the evacuated portion in a more distal distribution than after laparotomy alone. The acceleration of both courses, however, was of a temporary nature and took place, for the most part, during the first hour. Thereafter the differences were gradually equalized until complete correspondence was reached. This initial acceleration of both functions was surprising. The opposite condition would be more plausible, where the regional ischemia caused further paralysis of both gastric emptying and propulsive intestinal motility, when added to laparotomy.

It seems reasonable to regard the effect on the stomach as what is known as a long gastrointestinal reflex. Such a reflex, a gastroileal reflex, is elicited from the stomach, the increased motor activity of which is followed by a similar condition in the ileum (see Davenport, 1966). This type of gastrointestinal motility coordination has accordingly an *accelerative* effect and is polarized caudad. A gastroduodenal reflex where gastric distention *inhibits* duodenal motor activity was recently demonstrated by Daniel & Wiebe (1966).

If, on the other hand, the impulses proceed from receptors in the intestine, this has, as far as is known at present, a *paralysing* effect on the motor activity of both the stomach and the small intestine. Thus, distention of a distal intestinal loop causes paresis and dilatation of the stomach (ileogastric reflex).

In *moderate* ischemia a similar reflex might be initiated in the ischemic intestinal loop, and with the stomach as the effective organ, and there give rise to *increased* motor activity—more rapid emptying. When an increased amount of the contents of the stomach enters into the small intestine, it is subjected to a more rapid distal distribution, which can, consequently, be a direct result of the size of gastric emptying. Naturally, the possibility cannot be excluded that, in a similar manner, even the proximal small intestine is under the influence of the hypothetical long reflex, with increased propagative function. These questions

cannot be answered by means of the facts presented here, but they should lead to experiments being made with selective blockade of the autonomous nerve elements of the small intestine.

If, on the other hand, *pronounced* ischemia was produced in the small intestine, both gastric emptying and propagation in the intestine were retarded. This more logical condition, however, must be seen against the background that *moderate* ischemia had the contrary effect. One can only speculate about such possibilities as the functional elimination of the receptor area by local anoxia or that local intestinal paresis and dilatation produce an ileogastric reflex of the usual type, with paresis of the stomach and small intestine.

A condition, which the study of the gastric emptying and the quantitative distribution of the dose in the small intestine seems to make factual, is that, essentially, the latter function is dependent upon the former. If the intestine receives a large evacuated portion to work with, this is distributed distally to an extent proportional to its size. This condition can be asserted to hold good for all the analyses in these series. Thus, according to such a conception, the emptying mechanism of the stomach seems decisive, and distal propagation in the small bowel is essentially dependent upon the amount of material evacuated.

If this theory is analyzed by applying the mathematical method, the relation will become apparent to some extent. The greatly retarded emptying of the stomach after laparotomy is caused, as has been previously mentioned, either by total, initial passivity, which is followed by gradual reversion to a normal function, or by a slow emptying, which is in progress from the outset, and which likewise again becomes a normal function. Irrespective of this problem, the resumption by the stomach of a normal mathematical function has, in principle, a counterpart in the propagative function of the small intestine, but the stomach recovers its function *more rapidly* than does the small intestine, a condition which becomes more accentuated the longer the time that elapses.

The subjection of an intestinal loop to *moderate* ischemia, which initially leads to accelerated emptying of the stomach, does not have, according to this analytical method, any corresponding degree of accelerated distal distribution of the

evacuated portion. Thus, also here there is disproportion between the functions, which likewise becomes more pronounced when the emptying of the stomach, with prolonged experimental time, regains a normal mathematical function, whereas the propagation in the intestine is retarded in this respect. In principle, the same tendency is observed when the experimental ischemia is *pronounced*.

The mathematical analysis has supplemented the data obtained through this investigation, with an interesting fact that the propulsive motility in the small intestine, which, under normal conditions, is correlated with the emptying of the stomach, regains its normal function less rapidly than does the stomach, resulting in a comparatively proximal accumulation of the dose.

Summary

The question of how regional ischemia in the small intestine affects the propulsive motility of the gastrointestinal tract, was analyzed experimentally on rats.

In this connection regional ischemia was varied and quantitative analysis of propulsive motility carried out.

Graded ischemia was obtained by ligating a defined number of terminal vascular ramifications at the mesenteric border of the intestine. They were called mesenteric end arcades (mes end arc) and formed the connection between two adjacent secondary arches in the mesentery.

The vasculo-anatomic grading method was superior to simple measurement of the length of the devascularized segment.

The graded ischemia was correlated with the exchange circulation of the mucosa. The latter was evaluated indirectly as the elimination of radio-iodide from a central loop in the devascularized intestine. When the iodide concentration of the tracer solution and the iodide metabolism of the experimental animal were standardized, and the intestinal segment (mucosal surface) had a constant size, the exchange circulation of the mucosa was the only variable of significance in the passive absorption of the radio-iodide.

The *tail curve* represented the occurrence of radio-iodide in the tail of the experimental animal—the extravascular space. The slope was shown to be an indirect expression of the exchange circulation in the mucous membrane of the given loop.

There was a high correlation between the vasculo-anatomical gradation of the ischemia, on the one hand, and the elimination of the radio-iodide from the intestinal loop and the inclination of the tail curve, on the other.

It was only when 7 mes end arc had been ligated that the exchange circulation of the mucosa was significantly reduced. Propulsive motility was therefore analyzed in groups representing from 7 to 13 ligated mes end arc.

Iodide leakage through the ischemic intestinal

wall at maximal devascularization could be a source of error. It was determined by means of a special experimental model, called the "*double-rat*" technique. The transmural loss was insignificant.

Another point of similar importance was the possible occurrence of a peritoneal reaction causing reduction of permeability. This was recorded in *in vitro* experiments, where transmural iodide loss was analyzed following such experimental procedures as were otherwise applied to the material. This transmural loss of iodide decreased after laparotomy, probably as a result of an inflammatory reaction with exudation of fibrin.

When the intestine was subjected to ischemia, permeation of iodide through the wall increased in proportion to the severity of the ischemia. The impermeability caused by laparotomy and by the process inducing ischemia could not prevent the iodide from diffusing out.

Human serum albumin was hydrolyzed by proteolytic enzymes in the intestinal specimen, so that only iodide passed outwards through the intestinal wall. Permeability experiments with this substance gave, instead, information on the effect of ischemia on the proteolytic enzyme system of the intestine. The ischemic cell damage appeared to empty the epithelial cells of varying proportions of their enzyme contents.

In the most pronounced condition of ischemia, angiography demonstrated an anastomotic flow peripheral to the ligatures and on the surface of the intestine.

The intestinal villi had only a small part of the capillary area available for circulation. The rest was filled with blood, which had probably flowed back from the veins.

Laparotomy alone produced pronounced retardation of the emptying of the stomach. Only after 3–5 hours was it of the same degree as that characteristic of intact control animals after 1 hour.

The results of regional ischemia were compared with the conditions following laparotomy.

Moderate ischemia, with the ligation of 7-9 mes end arc, caused initial acceleration of gastric emptying. When the experimental period was prolonged the difference was eliminated. In *pronounced* regional ischemia, with the ligation of 11-13 mes end arc, gastric emptying was less effective in the later phase.

The quantitative distribution of the evacuated portion in the small intestine seemed to be dependent upon the extent to which the stomach was emptied. When this was initially slowed down, the insignificant, evacuated portion was distributed over a short, proximal section of the intestine. When the experimental period was prolonged and the emptying of the stomach was more effective, the distribution appeared to be proportionally more distally orientated.

Moderate regional ischemia, with initially accelerated emptying of the stomach, had a more distal distribution of the dose in the small bowel; this condition was equalized when the emptying of the stomach subsequently corresponded with that of the laparotomized control animals. A similar condition—relations between gastric empty-

ing and small intestinal propagation of the dose—seems also to occur in connection with *pronounced* ischemia.

It appeared justifiable to conclude that the extent to which the stomach is emptied determines the quantitative distribution of the evacuated portion of the dose in the small intestine.

Mathematical analysis with the special ratio method, however, modified this conclusion. It was found that, after initial passivity, the stomach resumed its mathematical function quicker than did the small intestine. This resulted in a comparative accumulation of the evacuated portion in the proximal parts of the small intestine. This condition applied both to groups only laparotomized and to those also subjected to surgical ischemia.

Moderate ischemia gave the most pronounced disproportion between the emptying of the stomach and intestinal propagation when, initially, the stomach was emptied most rapidly, so that the proximal accumulation in the small intestine was most pronounced.

References

- Aberdeen, V., Shepherd, P. A. & Simmonds, W. J. 1960. Concurrent measurement in unanesthetized rats of intestinal transport and fat absorption from the lumen. *Quart J Exp Physiol* 45, 265-274.
- Abramson, D. J. & Fierst, S. M. 1941. Peripheral vascular responses in man during digestion. *Amer J Physiol* 133, 686-693.
- Alvarez, W. C. 1948. *An Introduction to Gastroenterology*, 4th ed. P. B. Hoeber, Inc., New York.
- Amundsen, E. & Gustafsson, B. E. 1963. Results of experimental intestinal strangulation obstruction in germ-free rats. *J Exp Med* 117, 823-832.
- Amundsen, E. 1964. Studies on a toxicity-enhancing factor in fluid from experimentally strangulated intestinal loops in the rat. *J Surg Res* 4, 531-536.
- Amundsen, E. & Midtvedt, T. 1964. The toxicity of fluid from experimentally strangulated intestinal loops in the rat. *J Surg Res* 4, 306-313.
- Barlow, T. E. 1952. Vascular patterns in the alimentary canal. In *Visceral Circulation*. Ciba Foundation Symposia. J. & A. Churchill Ltd., London, p. 21.
- Barnett, W. O. 1960. Experimental strangulated intestinal obstruction. *Gastroenterology* 39, 34-40.
- Barry, H. C. 1942. Fibrous stricture of the small intestine following strangulated hernia. *Brit J Surg* 30, 64-69.
- Bashour, F. A. & McClelland, R. 1967. Splanchnic circulation in shock. *Gastroenterology* 52, 461-467.
- Bayliss, W. M. & Starling, E. H. 1899. The movements and innervation of the small intestine. *J Physiol* 24, 8-143.
- Bean, J. W. & Sidky, M. M. 1957. Effects of low O_2 on intestinal blood flow, tonus and motility. *Amer J Physiol* 189, 541-547.
- Berman, B., Braunstein, J. R. & McQuire, J. 1950. Effect of meals on electrocardiogram and ballistocardiogram in patients with angina pectoris. *Circulation* 1, 1017-1025.
- Berman, L. G. & Russo, F. R. 1950. Abdominal angina. *New Eng J Med* 242, 611-613.
- Blain, A. & Kennedy, J. D. 1946. The effect of penicillin in experimental intestinal obstruction. Studies on strangulated low ileal obstruction. *Bull Hopkins Hosp* 79, 1-20.
- Blalock, A. & Levy, S. E. 1939. Gradual complete occlusion of the celiac axis, the superior and inferior mesenteric arteries, with survival of animals: Effects of ischemia on blood pressure. *Surgery* 5, 175-178.
- Boley, S. J., Krieger, H., Schultz, L., Robinson, K., Siew, F. P., Allen, A. C. & Schwartz, S. 1965. Experimental aspects of peripheral vascular occlusion of the intestine. *Surg Gynec Obstet* 121, 789-794.
- Bradley, O. C. 1927. *Topographical Anatomy of the Dog*. Oliver & Boyd, London, pp. 27-28.
- Brandt, J. L., Castleman, L., Ruskin, H. D., Greenwald, J. & Kelly Jr., J. J. 1955. The effect of oral protein and glucose feeding on splanchnic blood flow and oxygen utilization in normal and cirrhotic subjects. *J Clin Invest* 34, 1017-1025.
- Brown, M. J. 1940. Mesenteric venous occlusion: A clinical entity. *Amer J Surg* 49, 242-249.
- Brunschwig, A., Bigelow, R. & Nichols, S. 1945. Elective occlusion and excision of the portal vein. *Surgery* 17, 781-785.
- Cannon, W. B. 1939. A law of denervation. *Amer J Med Sci* 198, 737-750.
- Code, C. F., Hightower Jr., N. C. & Morlock, C. G. 1952. Motility of the alimentary canal in man; review of recent studies. *Amer J Med* 13, 328-351.
- Code, C. F., Rogers, A. G., Schlagel, J., Hightower Jr., N. C. & Bagen, J. A. 1957. Motility patterns in the terminal ileum: Studies on two patients with ulcerative colitis and iliac stomas. *Gastroenterology* 32, 651-665.
- Cohn, Jr., I., Atik, M. & Werner, J. C. 1960. Strangulation obstruction: Combined arterial and venous strangulation. *Surgery* 48, 1006-1016.
- Cohn, Jr., I. & Atik, M. 1961. Strangulation obstruction—closed loop studies. *Ann Surg* 153, 94-102.
- Cooper, H. S. F. 1928. The cause of death in high obstruction. *Arch Surg* 17, 919-967.
- Councilman, W. T. 1894. Three cases of occlusion of the superior mesenteric artery. *Boston Med Surg J* 130, 410.
- Cummins, A. J. & Jussila, R. 1955. Comparison of glucose absorption rates in the upper and lower human small intestine. *Gastroenterology* 29, 982-992.
- Daniel, E. E. & Wiebe, G. E. 1966. Reciprocal inhibitory reflexes in stomach and duodenum. *Amer J Physiol* 211, 634-642.
- Davenport, H. W. 1966. *Physiology of the Digestive Tract*, 2nd ed. Year Book Medical Publishers Inc., Chicago, p. 67.
- Davis, D. M. & Stone, H. B. 1917. Studies on the development of toxicity in intestinal secretion. *J Exp Med* 26, 687-691.
- Davis, B. B. 1921. Thrombosis and embolism of the mesenteric vessels. *Nebraska Med J* 6, 101-104.
- Davis, H. A., Gaster, J., Marsh, R. L. & Pritel, P. A. 1948. The effect of streptomycin in experimental strangulation of the bowel. *Surg Gynec Obstet* 87, 63-67.
- Derblom, H. & Nylander, G. 1963. Uptake from the small intestine to the peripheral circulation of $Na^{131}I$ and ^{131}I -labelled human serum albumin in the rat under varying experimental conditions. *Acta Chir Scand* 125, 147-161.

- Derblom, H., Johansson, H. & Nylander, G. 1963. Thyroid hormone activity and gastrointestinal functions. An experimental study in the rat. *Acta Chir Scand Suppl* 307.
- 1966. A simple method of recording quantitatively certain gastrointestinal motility functions in the rat. *Acta Chir Scand* 132, 154–165.
- Dieulafe, R. 1936. Contribution à l'étude de l'irrigation de l'intestin grêle—Consequences de la ligature expérimentale des vaisseaux mésentériques. *Arch Anat (Strasb)* 21, 97–108.
- Dragstedt, L. R., Moorehead, J. J. & Burcky, F. W. 1917. Intestinal obstruction. An experimental study of the intoxication in closed intestinal loops. *J Exp Med* 25, 421–439.
- Dragstedt, L. R. & Dragstedt, C. 1922. Acute dilatation of the stomach. *J A M A* 79, 612–615.
- Dragstedt, C., Lang, V. F. & Millet, R. F. 1929. The relative effects of distention on different portions of the intestine. *Arch Surg* 18, 2257–2263.
- Dunphy, I. E. 1936. Abdominal pain of vascular origin. *Amer J Med Sci* 192, 109–113.
- Dwight, T. 1903. The branches of the superior mesenteric artery to jejunum and ileum. *Anat Anz* 23, 184–186.
- Enríques de Salamanca, F. & Picazo, J. 1942. Extracciones seriadas del te de prueba en sujetos normales. *Trab Inst nac cienc med (Madrid)* 1, 3–14.
- Eisberg, H. B. 1924. Intestinal arteries. *Anat Rec* 28, 227–242.
- 1925. On the viability of the intestine in intestinal obstruction. *Ann Surg* 81, 926–938.
- Farrar, J. T., Zworykin, V. K. & Baum, J. 1957. Pressure-sensitive telemetering capsule for study of gastrointestinal motility. *Science* 126, 975–976.
- Folkow, B. 1949. Intravascular pressure as a factor regulating the tone of the small vessels. *Acta Physiol Scand* 17, 289–310.
- Folkow, B. 1960. Role of the nervous system in the control of vascular tone. *Circulation* 21, 760–768.
- Folkow, B., Lundgren, O. & Wallentin, I. 1963. Studies on the relationship between flow resistance, capillary filtration coefficient and regional blood volume in the intestine of the cat. *Acta Physiol Scand* 57, 270–283.
- Folkow, B., Lewis, D. H., Lundgren, O., Melander, S. & Wallentin, I. 1964 a. The effect of graded vasoconstrictor fibre stimulation on the intestinal resistance and capacitance vessels. *Acta Physiol Scand* 61, 445–457.
- 1964 b. The effect of the sympathetic vasoconstrictor fibres on the distribution of capillary blood flow in the intestine. *Acta Physiol Scand* 61, 458–466.
- Folkow, B. 1967. Regional adjustments of intestinal blood flow. *Gastroenterology* 52, 423–432.
- Forty, F. 1957. Mesenteric vascular occlusion. *Brit J Surg* 44, 458–460.
- García, J. D. 1927. *Rev méd cubana* 38, 386.
- Garré, C. 1892. Ueber eine eigenartige Form von narbiger Darmstenose nach Brucheingklemmung. *Beitr klin Chir* 9, 187–197.
- Ginzburg, L. & Klein, E. 1928. Late intestinal stenosis following strangulated hernia. *Ann Surg* 88, 204–211.
- Ginzburg, L. & Oppenheimer, G. D. 1933. Non-specific granulomata of the intestines. *Ann Surg* 98, 1046–1062.
- Glotzer, D. J., Villegas, A. H., Anekamaya, S. & Shaw, R. 1962. Healing of the intestine in experimental bowel infarction. *Ann Surg* 155, 183–190.
- Grevsten, S., Johansson, H. & Nylander, G. 1967. Analysis of a quantitative method of evaluation as applied to the propulsive gastrointestinal motility in the rat. *Acta Chir Scand* 133, 563–567.
- Grim, E. & Lindseth, E. O. 1958. Distribution of blood flow to the tissues of the small intestine of the dog. *Univ Minn Med Bull* 30, 138–145.
- Grollman, A. 1929. Physiological variations in the cardiac output of man. III. The effect of the ingestion of food on the cardiac output, pulse rate, blood pressure, and oxygen consumption of man. *Amer J Physiol* 89, 366–370.
- Guthrie, J. E. & Quastel, J. H. 1956. Absorption of sugars and amino acids from isolated surviving intestine after experimental shock. *Arch Biochem* 62, 485–496.
- Hanson, K. M. & Johnson, P. C. 1962. Evidence for local arteriovenous reflex in intestine. *J Appl Physiol* 17, 509–513.
- Harper, W. H. & Blain, A. 1945 The effect of penicillin in experimental intestinal obstruction. *Bull Hopkins Hosp* 76, 221–244.
- Hawkins, G. K., Margolin, S. & Thompson, J. J. 1953. Gastric emptying time: Comparative studies with placebos, Prantal and Banthine. *Gastroenterology* 24, 193–199.
- Herrick, J. F., Essex, H. E., Mann, F. C. & Baldes, E. J. 1934. The effect of digestion on the blood flow in certain blood vessels of the dog. *Amer J Physiol* 108, 621–628.
- Hightower Jr., N. C. 1959. Motility of the alimentary canal of man. In *Disturbances in Gastrointestinal Motility*. Ch. C. Thomas, Springfield, III, pp 3–61.
- Hunt, J. N. & Spurrel, W. R. 1951. The pattern of emptying of the human stomach. *J Physiol* 113, 157–168.
- Hurwitt, E. S., Altman, S., Borow, M. & Rosenblatt, M. 1953. Intraabdominal arterial anastomoses. An experimental study. *Surgery* 34, 1043–1060.
- Johansson, H. 1966. Gastrointestinal motility function related to thyroid activity. *Acta Chir Scand Suppl* 359.
- Johansson, H. & Nylander, G. 1968. Analysis of the ileo-cecal passage in the rat. *Acta Chir Scand*. In press.
- Johnson, P. C. 1960. Autoregulation of intestinal blood flow. *Amer J Physiol* 199, 311–318.
- Johnson, P. C. & Hanson, K. M. 1962. Effects of arterial pressure on arterial and venous resistance of the intestine. *J Appl Physiol* 17, 503–508.
- Johnson, P. C. 1965. Effect of venous pressure on mean capillary pressure and vascular resistance in the intestine. *Circ Res* 26, 294–300.
- Kampp, M. & Lundgren, O. 1966 a. Blood flow and flow distribution within the small intestine of the cat. *Acta Physiol Scand* 68, Suppl. 277.

- 1966 b. Evidence for countercurrent exchange in intestinal villi. *Acta Physiol Scand* 68, Suppl. 277.
- Klein, E. 1921. Embolism and thrombosis of the superior mesenteric artery. *Surg Gynec Obstet* 33, 385–405.
- Laufman, H. 1943. Gradual occlusion of the mesenteric vessels *Surgery* 13, 406–410.
- Laufman, H. & Method, H. 1947. The rôle of vascular spasm in recovery of strangulated intestine. *Surg Gynec Obstet* 85, 675–686.
- Laufman, H., Martin, W. B. & Tuell, S. W. 1948. The pattern of vasospasm following acute arterial and venous occlusions. *Surg Gynec Obstet* 108, 347–350.
- Laufman, H. 1950. Experimental evidence of factors concerned in the eventual recovery of strangulated intestine: Effects of massive penicillin therapy. *Surgery* 28, 509–515.
- Lillehei, R. C., Goott, B. & Miller, F. A. 1959. The physiological response of the small bowel of the dog to ischemia including prolonged *in vitro* preservation of the bowel with successful replacement and survival. *Ann Surg* 150, 543–559.
- Lindquist, B. 1968. Propulsive gastrointestinal motility related to retroperitoneal irritation. *Acta Chir Scand.* Suppl. 384.
- Loewe, L., Hirsch, E. & Grazel, D. M. 1947. The action of heparin on experimental venous thrombosis. *Surgery* 22, 746–760.
- Lundgren, O. & Kampp, M. 1966. The wash-out of intra-arterially injected krypton⁸⁵ from the intestine of the cat. *Experientia* 22, 268.
- MacKay, R. S. & Jacobson, B. 1957. Endoradiosonde. *Nature* (London) 179, 1239.
- Marbaix, O. 1898. Le passage pylorique. *Cellule* 14, 251–331.
- Martin, W. B., Laufman, H. & Tuell, S. M. 1949. Rationale of therapy in acute vascular occlusions based upon micrometric observations. *Ann Surg* 129, 476–493.
- Meier, A. L. & Waibel, P. 1964. Mesentery occlusion with intestinal gangrene. *Arch Surg* 88, 45–48.
- Mikkelsen, W. P. 1957. Intestinal angina: Its surgical significance *Amer J Surg* 94, 262–269.
- Monks, G. H. 1905. Studies in the surgical anatomy of the small intestine and its mesentery. *Ann Surg* 42, 543–569.
- 1909. Intestinal localization. *JAMA* 52, 1079–1086.
- 1929. Intestinal localization. *Surg Gynec Obstet* 49, 213–229.
- Moore, T. 1941. Mesenteric vascular occlusion. *Brit J Surg* 28, 347–356.
- Nelson, L. E. & Kremen, A. J. 1950. Experimental occlusion of the superior mesenteric vessels with special reference to the rôle of intravascular thrombosis and its prevention by heparin. *Surg Gynec Obstet* 28, 819–826.
- Noer, R. J. & Manning, J. E. 1941. A comparative study of the small intestinal circulation. *Trans West Surg Ass* 272–285.
- Nylander, G. & Olerud, S. 1960. A simple microangiographic procedure for study of the vascular pattern in the alimentary canal. *Acta Soc Med Upsal* 65, 374–388.
- 1961. The vascular pattern of an isolated jejunal loop. *Acta Chir Scand* 121, 39–46.
- Nylander, G. & Wikström, S. 1967. Gastric emptying and propulsive intestinal motility following partial gastric resections, gastroenteroanastomosis, and abdominal “trunk” vagotomy in the rat. *Acta Chir Scand* 133, 41–54.
- Nylander, G. 1967. Gastric evacuation and propulsive intestinal motility following resection of the small intestine in the rat. *Acta Chir Scand* 133, 131–138.
- Nylander, G. & Svensson, A. 1968. Gastric emptying and propulsive intestinal motility in experimental intestinal obstruction. *Acta Chir Scand.* In press.
- Ortner, N. 1903. Zur Klinik der Angiosklerose der Darmarterien. (Dyspragia intermittens angiosclerotica intestinalis). *Samml klin Vortr* 347 (Innere Med Nr 102) 855–904.
- Paine, R. M. & Shock, N. W. 1950. Variability of cardiac output estimations made with high-frequency undamped ballistocardiograph. *Circulation* 1, 1026–1031.
- Raw, S. C. 1943. Stricture of small bowel following strangulated hernia. *Lancet* 244, 460.
- Rayner, R. R., MacLean, L. D. & Grim, E. 1960. Intestinal tissue blood flow in shock due to endotoxin. *Circ Res* 8, 1212–1217.
- Reich, A. 1913. Embolie und Thrombose der Mesenterialgefäße, *Ergebn Chir Orthop* 7, 515–597.
- Reininger, E. J. & Sapirstein, L. A. 1957. Effect of digestion on distribution of blood flow in the rat. *Science* 126, 1176.
- Reynell, P. C. & Spray, G. H. 1956. The simultaneous measurement of absorption and transit in the gastrointestinal tract of the rat. *J Physiol* 131, 452–462.
- Rives, J. D., Strug, L. H. & Essrig, I. M. 1948. Mesenteric vascular occlusion. *Ann Surg* 127, 887–905.
- Robb, H. J., Jacobson, L. F. & Jordan Jr., P. 1965. Microvascular changes during the interruption and re-establishment of circulation. *J Trauma* 5, 341–347.
- Rosenthal, S. & Nasset, E. S. 1958. Gastric emptying and intestinal absorption of carbohydrate and protein as influenced by the nature of the test meal. *J Nutr* 66, 91–103.
- Sarnoff, S. J. & Poth, E. J. 1944. Protective action of sulfasuxidine following simple mesenteric venous occlusion. *Surgery* 16, 927–931.
- Sarnoff, S. J. & Fine, J. 1945. The effect of chemotherapy on the ileum subjected to vascular injury. *Ann Surg* 121, 74–82.
- Scott, H. G. & Wangenstein, O. H. 1932. Length of life following various types of strangulation obstruction in the dog. *Proc Soc Exp Biol Med* 29, 424–427.
- Sidky, M. & Bean, J. W. 1958. Influence of rhythmic and tonic contractions of intestinal muscle on blood flow and blood reservoir capacity in dog intestine. *Amer J Physiol* 193, 386–392.
- Stone, H. B., Bernheim, B. M. & Whipple, G. H. 1912. Intestinal obstruction: A study of the toxic factors. *Bull Hopkins Hosp* 23, 159–165.
- Sögnen, E. 1965. Effects of calcium-binding substances on gastric emptying as well as intestinal transit and absorption in intact rats. *Acta Pharmacol* 22, 31–48.

- Tamarit, T. J. & Enríques de Salamanca, F. 1952. La fisiología gástrica del perro. *Arch Med Exp* (Madrid) 15, 303-318.
- Texter, Jr., E. C., Vantrappan, G., Liemer, M. D. & Barborka, C. J. 1958. Methods for studying gastrointestinal motility. *Quart Bull Northwest Univ Med Sch* 32, 281-290.
- Thomas, J. E. 1955. The gradient theory versus the reflex theory of intestinal peristalsis. *Amer J Gastroent* 23, 13-25.
- Thornton, G. H. M., Bean, W. B. & Hodges, R. E. 1955. The effect of pantothenic acid deficiency on gastric secretion and motility. *J Clin Invest* 34, 1085-1091.
- Tiedemann, F. 1843. *Von der Verengerung und Schliessung der Pulsadern in Krankheiten*. Heidelberg u Leipzig, p. 131.
- Turner, M. D., Grogan, J. B. & Truett, G. W. 1961. A study of the lethal mechanism in experimental closed-loop strangulated obstruction of the small intestine. *Amer J Surg* 102, 560-568.
- Varró, V., Blahó, G., Csernay, L., Jung, I. & Szarvas, F. 1965. Effect of decreased local circulation on the absorptive capacity of a small-intestine loop in the dog. *Amer J Dig Dis* 10, 170-177.
- Varró, V., Jung, I., Szarvas, F., Csernay, L., Sávy, G., & Ökrös, J. 1967 a. The effect of vasoactive substances on the circulation and glucose absorption of an isolated jejunal loop in the dog. *Amer J Dig Dis* 12, 46-59.
- Varró, V., Csernay, L., Szarvas, F. & Blahó, G. 1967 b. Effect of glucose and glycine solution on the circulation of the isolated jejunal loop in the dog. *Amer J Dig Dis* 12, 60-64.
- Virchow, R. 1854. Verstopfung der Gekrösarterie durch einen eingewanderten Propf. *Verh phys-med Ges Würzb* 40, 341-349.
- Wangenstein, O. H. 1937. *The Therapeutic Problem in Bowel Obstruction*. Ch. C. Thomas, Springfield, Ill., pp 24-25.
- Weyrauch, Helen, B. & De Garis, C. F. 1937. Normal and interrupted vascular patterns in the intestinal mesentery of the rat. An experimental study on collateral circulation. *Amer J Anat* 61, 343-372.
- Wikström, S. 1968. Propulsive gastrointestinal motility in regional and graded ischemia of the small bowel. An experimental study in the rat. II. Late results. *Acta Chir Scand*. Suppl. 386.
- Yull, A. B., Abrams, J. S. & Davis, J. H. 1962. The peritoneal fluid in strangulation obstruction. The role of the red blood cell and *E. coli* bacteria in producing toxicity. *J Surg Res* 2, 223-232.

ACTA CHIRURGICA SCANDINAVICA

SUPPLEMENTUM 386

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Propulsive gastrointestinal
motility in regional
and graded ischemia of
the small bowel

*An experimental study in the rat
II. Late results*

by STIG WIKSTRÖM

STOCKHOLM 1968

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Introduction

Many diseases with symptoms from the abdominal organs have a vascular origin. Clinical observations and animal experiments have shown that insufficiency of the mesenteric circulation affects gastrointestinal functions more frequently and to a greater degree than is generally supposed. Previously, it has been mainly the effect of the interruption of flow in the main mesenteric vessels that has been studied. Less attention has been paid to the effect of regional intestinal ischemia,

with cessation of flow in the *small* vessels at, and distal to, the last mesenteric ramifications. The direct and immediate effect of regional and graded intestinal ischemia on the gastrointestinal propulsive motility has been studied extensively by Nylander & Wikström (1968).

The aim of the present investigation was to ascertain the corresponding effect of such differentiated and regional ischemia during a period of up to 14 days after its surgical induction.

Chapter I. Review of the Literature

The fate of an intestine that has sustained circulatory damage depends largely on the localization and extent of the current vascular occlusion. The architectonics of the mesenteric and intramural vessels of the small intestine are such that they afford protection, to a substantial extent, against circulatory disturbances that constitute a threat to its vitality.

A series of investigations carried out mainly on dogs has shown that the small intestine is affected by total and irreversible necrosis after about 4 hours when its arterial circulation is suddenly and totally occluded (Nelson & Kremen, 1950; Medins & Laufman, 1958; Lillehei *et al.*, 1959, and others). Glotzer *et al.* (1959) stated that this occurred after 7 hours, but they used a shorter, isolated segment of the intestine requiring nearly twice as long an ischemic period before irreparable damage took place.

Occlusions of large mesenteric vessels are probably much rarer than occlusive changes in *small* vessels at, and distal to, the vascular arches (Boley *et al.*, 1965). The blocking of these at different levels caused differentiated pathological changes in the intestine ranging from mucosal oedema, via superficial and penetrating wounds, to segmental

infarction with total intestinal necrosis. Boley *et al.* drew the conclusion that the vascular changes which occur in connection with unspecific small-intestinal wounds are primary, and the inflammatory changes secondary. They suggested that there may be a vascular component in the genesis of such chronic diseases as regional enteritis, ulcerative colitis etc.

When blood ceases to flow to a tissue the outcome depends primarily on how rapidly collateral circulation is developed. The superior mesenteric artery has collateral connections with the coeliac artery and the inferior mesenteric artery. These are not sufficient, however, to supply the intestine if the main trunks are suddenly blocked. On the other hand, the intestine can survive if the obstruction develops over a longer period (Blalock & Levi, 1939).

The important role of the collateral circulation has been documented in connection with animal experiments, especially by Lillehei *et al.* (1959). When all the collaterals of the superior mesenteric artery were ligated at the same time as the main artery, the survival time was only half of that when the main artery alone was ligated.

Similarly, Laufman (1943) showed that when

the superior mesenteric vein was gradually ligated in the same way, a collateral system was developed, which maintained the circulation of the intestine and kept it vital. Thus, to the extent that the collateral vascular system has time to develop, the vitality of the intestine can be saved.

Virchow (1854) was the first to emphasize the importance of maintaining a satisfactory central circulation for the survival of an intestine that has sustained circulatory damage. The collateral circulation can compensate for the loss of large mesenteric vessels, but if the central circulation fails, the collaterals are decompensated, which results in intestinal necrosis. This occurs in heart failure, haemorrhagic shock or fall in blood pressure due to some other cause.

Spontaneous healing may occur in cases with occlusion of the large mesenteric vessels (Karcher, 1897; Reed, 1921; Moore, 1941). In such a situation the collateral circulation can suffice to protect the intestine from destruction, but the normal motility function may not be maintained (Councilman, 1894; Reich, 1913; Davis, 1921; Garcia, 1927).

The absorption capacity of the intestine often becomes defective as a result of vascular intestinal damage, and a condition of pronounced malnutrition can arise (Ortner, 1903; Klein, 1921; Dunphy, 1936; Berman & Russo, 1950).

It has been known for a long time that a small intestine which has sustained circulatory damage often heals with the formation of scars and strictures (Garré, 1892; Ginzburg & Klein, 1928; Ginzburg & Oppenheimer, 1933; Barry, 1942; Raw, 1943; Hurvitt *et al.*, 1953, and others). The mucous membrane is damaged, becomes ulcerated and desquamates, local infection occurs and healing subsequently results in strictures. Rosenman & Gropper (1955) described tubular stenosis of the small intestine following occlusion of the mesenteric vessels. They considered that scars and strictures occurred according to the same principles as in strangulated hernia, where the causal connection was previously pointed out by Wangensteen (1942).

In 1921 Klein reported a detailed, experimental study on the dog, where, after producing graded ischemia, he was able to show a scale of ischemic changes from restricted necrosis of the mucous membrane to widespread infarction of all the mural layers of the intestine. He con-

sidered that the changes corresponded to what is observed when the mesenteric vessels undergo thrombo-embolic occlusion. Laufman (1950) demonstrated in dogs that scarred tissue with stenosis and ileus can result from severe damage to the intestinal wall, following circulatory disturbances. These experimental results verify the previous clinical observations that an intestine which has sustained circulatory damage survives, but either does not recover its normal peristaltic function – physiological “stricture” (Raw, 1943) or is so severely changed by scars that strictures and difficulties in passage occur (Garré, 1892; Barry, 1942; Raw, 1943; Grisell, 1949; Wangensteen, 1942).

Chapter II. The Experimental Animal

GENERAL ASPECTS

The albino rat was chosen for several reasons. The experimental technique applied in this investigation required extensive animal material, and consequently it was desirable to use a small, inexpensive animal. The rat is suitable for quantitative analysis of the gastrointestinal propulsive motility, with the method that was available.

Adult albino rats were used (over 200 g). They belonged to the same strain (Sprague-Dawley) and were all males. They were not used until at least one week after they had been delivered. They were fed with a diet produced by AB Ewos, Södertälje, Sweden. The diet was standardized in respect to calories, minerals and vitamins. The iodine content was stated to be 0.00006% of weight.

ASPECTS OF THE GASTROINTESTINAL TRACT IN THE RAT

The rat stomach is divided into two distinct parts, the cardiac and the pyloric portions. The former comprises the upper part of the organ and functions as a reservoir for the stomach. It has a mucosa with squamous epithelium, extremely thin muscle layers, an inner circular and an outer longitudinal layer as well as serosa. Secretory function is entirely absent. The lower part of the stomach, the pyloric portion, has, on the other hand, an active glandular epithelium and strong muscle layers. This part provides the stomach with secretory and motor activity. Gastric emptying is performed by peristaltic contractions of constant frequency. Consequently, a good idea of the mean activity of the stomach is obtained by analyses during a limited period of time.

The length of the small intestine of rats weighing between 200 and 300 g is said to be about 100 cm. It discharges into the lower part of the caecum. Normal transport in the intestine is most rapid in its upper part and is increasingly slower farther down.

The vascular architectonics of the small in-

testine vary somewhat. In the mesenterium the number of intestinal arteries varies between 15 and 19 (Weyrauch & De Garis, 1937). The arteries are given off from the main trunk, proximally, at shorter intervals than lower down. Therefore, in the terminal ileum each intestinal artery supplies a longer segment of the intestine than higher up. During their course to the mesenteric attachment the arteries divide into what are known as primary arches. The mesenterium has about 45 of these primary vascular arches. After the formation of another arch, straight arteries are given off which run to the mesenteric attachment of the intestine. When a primary arch divides into two secondary arches a bifurcation is formed, which is called here, as in a previous work (Nylander & Wikström, 1968), a mesenteric end arcade.

From the secondary arches arise the vasa recta, which divide into two vessels at the mesenteric attachment. These vessels undergo further ramification on the surface of the intestine, penetrate its wall and extend intramurally. The anatomical and physiological conditions in the gastrointestinal tract of the rat have been described in detail by Griffith & Farris (1942), Shay *et al.* (1945), Hunt (1959), Fock (1962) and Parkkulainen (1962).

Chapter III. Comments on Material and Operation Technique

MATERIAL

Before the experiments the animals were fasted for 18 hours with free access to water. All operative procedures were carried out under ether anaesthesia. The animals were placed in closed glass containers with gauze compresses soaked in ether until they were anaesthetized, after which anaesthesia was maintained with a minimum of ether on an open mask. At completion of the operation the animals were awake. The operation area was washed with 7% tannin in 70% alcohol. The operations were performed under clean but not sterile conditions.

METHOD OF OBTAINING SURGICAL ISCHEMIA

As in the previous work (Nylander & Wikström, 1968), standardized and graded ischemia was obtained in this case by ligating 7 or 11 mesenteric end arcades, defined in Chapter II. The abbreviation mes end arc will be used to denote this concept. The ligatures were always made immediately proximal to the mes end arc. The material used for the ligatures was 5/0 cardiovascular silk (Ethicon). The first ligature was made at the 7th mes end arc counting from the ileo-caecal angle; and from here the given number of mes end arc were ligated in a proximal direction.

Chapter IV. Quantitative Evaluation of the Standardized Ischemia

Surgically produced ischemia in a defined intestinal loop was thus graded anatomically by stating the number of ligated mes end arc. Such anatomic gradation was correlated, as previously, with a more exact quantitative evaluation. This was based on the hypothesis that passive absorption of a substance from a small intestinal loop of defined size, is an expression of the effective exchange circulation in its mucous membrane. In this case a radioactive iodide isotope was used as the test substance. Its elimination from the loop subjected to surgical ischemia was regarded as representing the capillary circulation in the mucous membrane of the loop. The procedure has been described in detail in a previous work, where its basic principles and reliability have been discussed in detail (Nylander & Wikström, 1968).

MATERIAL AND METHODS

This part of the investigation comprised animals where 7 mes end arc were ligated as previously described. The effect of this surgical ischemia

was then investigated after 7 and 14 days, respectively. As control material, animals were used that had only been laparotomized: laparotomized controls (LC). Since the effect of the laparotomy was supposed to be entirely eliminated after 14 days the LC group was only analyzed 7 days after the operation had been performed.

For this part of the investigation 56 animals were used. In accordance with what has been stated above, this material was divided into 3 groups designated LC-7 days, 7 mes end arc-7 days, and 7 mes end arc-14 days. Table I shows the distribution of the animals into these three groups, and also the mean values for body weight, stomach weight and weight of the isolated intestinal loop.

All these animals were given additional iodide in their drinking water during the entire experimental period (5 drops of 0.33% iodide solution/100 ml of drinking water).

Radioactive sodium iodide (NaI^{131}) was used as the test substance. To obtain a standardized concentration gradient from the intestinal lumen

TABLE I. *Characteristics of the material*

Experimental group		n	Weight (g)			
			Isol. loop	Stomach	Body	
					Initial	Final
L C	7 days	15	0.9±0.03	3.3±0.21	214±1.5	204±2.6
7 mes end arc	7 days	20	0.9±0.02	2.8±0.12	228±4.5	213±4.8
7 mes end arc	14 days	21	0.9±0.02	3.4±0.10	237±6.3	237±5.8

to the capillary blood in this material, standardized in respect of iodide metabolism, a defined amount of carrier was always added. Thereby a specific activity of 30 $\mu\text{Ci}/100\ \mu\text{g}$ of iodide was obtained. The original solution was diluted so that at the beginning of the experiment 0.10 ml of the solution contained 10 μCi . In each case 0.10 ml of this solution was employed. The volume was measured with weighed tuberculin syringes, with a calculated reliability of $\pm 5\%$. The radioactivity in the measured volume was recorded before each experiment.

After the relevant part of the small intestine had been identified and 7 mes end arc ligated, as previously described, the extent of a central loop in the devasculated segment was indicated with threads. At analysis, 7 days after induction of ischemia, these were tied around the intestine without involving the terminal, vascular bifurcations. The portion of the intestine that was thus separated by ligatures, always had a length corresponding to 2 mes end arc. In the LC group the isolated loop of the intestine was of the same length. The location chosen was such that the distal ligature was at a distance from the ileo-caecal angle corresponding to 10 mes end arc.

Finally, a ligature (5-0 cardiovascular silk) was placed around the pylorus to prevent the contents of the stomach from passing into the small intestine.

In the part of the intestine thus isolated by ligation from continuity with the rest of the intestine, the radioactive dose was deposited intraluminally by means of transmural injection. For this a fine needle was used (Record No. 16). Immediately after withdrawal of the needle through the intestinal wall a filter paper was put over the insertion site. Its radioactivity was recorded, and was in no case higher than that of the background level.

Thereafter the abdominal wound was closed and, as a rule, the animal had awakened from the anaesthesia when the last sutures were sewn. After this the animal was kept in a separate cage, and killed after 30 minutes (with ether). The abdomen was opened and the stomach isolated by ligation at the cardia. It was then excised as also was the isolated intestinal loop where the dose had been deposited. Both specimens were weighed (Table I) and the radioactivity in each recorded (Table II). Thereafter the radioactivity in the remaining part of the body was determined (Table II). In every case double recordings were made, each comprising no fewer than 10,000 impulses.

DISCUSSION

The experimental method has been discussed in detail previously (Nylander & Wikström, 1968). A short summary is only given here.

The elimination of a diffusible, water-soluble substance from the lumen of the intestine to the capillary blood is dependent essentially upon two factors:

- 1. The concentration gradient of the substance between the two spaces.
- 2. The size of the contact area between the same spaces.

This in turn is dependent upon the size of the mucosal surface and its available capillary area.

Note 1: The radioactive test solution administered had a constant iodide concentration in all the experiments. Moreover, the animals were, from the point of view of iodide metabolism, strictly standardized. They belonged to the same strain, were of the same age and weight class, were given the same food and additional iodide in their drinking water. Iodide can be trapped in the thyroid gland and in the stomach. The standardized supply of iodide to the experimental animals eliminated any significant loss in the thyroid

TABLE II. Percentile distribution of the radioactive dose (NaI^{131}) in the experimental animal 30 min. after its deposition in the isolated intestinal loop. Mean values with S.E.

Experimental group		n	% of dose			Total absorption	% of total absorption trapped in the isolated stomach
			Isol. loop	Stomach	Body		
L C	7 days	15	40 ± 3.9	4 ± 0.5	56 ± 3.8	60	7
7 mes end arc	7 days	20	73 ± 2.6	1 ± 0.3	26 ± 2.4	27	4
7 mes end arc	14 days	21	75 ± 3.1	2 ± 0.7	23 ± 2.9	25	8

gland (Derblom, Johansson & Nylander, 1963). The secretion of iodide from the gastric mucosa was trapped in the stomach owing to the pyloric ligature. Thereby this part of the dose was prevented from emptying into the small intestine, and from there being absorbed. Instead, its size could now be quantitatively determined.

No significant excretion of radio-iodide occurred through the kidneys or salivary glands during the experimental period (Derblom, Johansson & Nylander, 1963).

Note 2: The intestinal loop into which the dose of radioactive iodide was deposited was of constant size throughout the entire series of experiments. It was, moreover, always situated centrally in the devascularized intestinal area. Within this area the supporting function of the anastomoses was probably at its weakest and, consequently, the circulation was at its worst.

The effects on the splanchnic circulation, which are produced by the anaesthesia, the operative procedure and other manipulations necessary for conducting the experiment, which were strictly standardized, were assumed to be the same for the whole animal material.

Thus, the only factor that distinguished the experimental groups was the alteration in the exchange circulation, which may have arisen as a result of the surgical ischemia and the time that this was allowed to continue. The elimination of the test dose from the defined loop of the small intestine should thus be an acceptable, indirect expression of the exchange circulation in the mucous membrane in the respective experimental groups.

RESULTS

The percentage distribution of the radioactive dose is reported with respect to the following:

1. The isolated loop of the small intestine = the unabsorbed part of the dose.
2. The isolated stomach = the part of the dose absorbed, and secreted by the gastric mucosa.
3. The rest of the body = the remaining, absorbed part of the dose.

The sum of the measurements according to points 2 and 3 represents the total absorption from the loop.

Table II shows that in group LC-7 days 40% of the radioactive dose remained unabsorbed after 30 minutes, and that 4% had been secreted into the stomach. In the group 7 mes end arc-7 days the corresponding elimination of the dose was much less. Thus, 73% of the radioactive dose remained in the isolated loop, and only 1% was secreted into the stomach. The group 7 mes end arc-14 days had practically the same percentage distribution of the radioactive dose. Thus 75% of the dose remained in the isolated loop, and secretion into the stomach was 2%.

If secretion of the radio-iodide by the stomach is expressed in per cent of the absorbed portion of the dose, nearly the same values were obtained for the two groups LC-7 days and 7 mes end arc-14 days, *i.e.* 7% and 8% respectively. In the group 7 mes end arc-7 days only 4% was secreted by the gastric mucosa.

DISCUSSION

It was previously demonstrated that the absorption of radio-iodide from the isolated loop was increasingly reduced the greater the number of the mesenteric vessels ligated (Nylander & Wikström, 1968). The gradual reduction of the total capillary area, which occurred when an increased number of mesenteric vessels were occluded, was considered to be the decisive factor.

In this work the effect of only a *moderate*

degree of ischemia on absorption was evaluated. Furthermore, this evaluation was made only at later stages, 7 and 14 days after vascular occlusion had been established.

Nylander & Wikström (1968) showed that, in immediate connection with the laparotomy, in the LC group, only 15% of the radioactive dose was still present in the isolated loop after 30 minutes. On the other hand, when the analysis was made, as in this case, 7 days after laparotomy was performed, then a much larger part (40%) of the dose remained unabsorbed in the loop. Laparotomy alone, performed 7 days before, had made the prerequisites decidedly less favourable for the absorption of the radio-iodide from the loop.

In a similar way, in the group 7 mes end arc, about 40% of the dose was not absorbed from the intestinal loop after 30 minutes (Nylander & Wikström, 1968). After 7 days, however, the non-utilized part of the dose remaining in the intestinal loop was about 70%.

After another 7 days, *i.e.* 14 days after the ischemic procedure, the distribution of the dose was about the same.

As regards the cause of the reduced iodide absorption, resulting from laparotomy performed 7 days previously, this cannot be elucidated by means of the available observations. It is reasonable to assume that inflammatory changes leading to fibrosis could create such a decrease in the effective exchange circulation of the mucous membrane of the intestinal loop, as was demonstrated here. The fibrotic changes may be localized in the intestinal wall (including the mucosa) or situated peripherally in the mesentery. A combination of both these conditions is, of course, conceivable. With regard to the investigation, this is of minor importance, as long as the effect of laparotomy is defined when the effects of the ischemic intestinal damage are to be evaluated.

When the intestinal loop was subjected surgically to such a degree of ischemia as corresponds to that produced by ligating 7 mes end arc, the iodide absorption was manifestly retarded. After 7 days the iodide absorption was retarded to a still greater extent, so that slightly over 70% of the dose remained unused. The corresponding effect of laparotomy resulted in a dose retention of 40%. Consequently, it is reasonable to assume that the inability of the loop to absorb the difference

(slightly over 30%) can be ascribed to the regional ischemia. The lapse of a further 7 days did not change these conditions; the iodide absorption from the isolated intestinal loop was the same. The following theoretical explanations may be valid. On the one hand, the effect of the operative procedure that causes vascular damage can remain unchanged after 14 days, at the same time as the effect of laparotomy also remains unchanged in comparison with the conditions after 7 days. On the other hand, the effect of the intervention that causes vascular damage may further diminish the absorption of iodide from the loop, and to the same extent as the corresponding effect of laparotomy is decreased.

The iodide secretion of the stomach after 7 and 14 days, expressed in per cent of the absorbed radio-iodide (see Table II), was less than that when the analysis of the corresponding groups was made immediately, *i.e.* 30 minutes after the vascular damage (Nylander & Wikström, 1968).

In an earlier study (Nylander & Wikström, 1968) an analysis was made according to the "double-rat" procedure, in order to ascertain the possibility of the radio-iodide diffusing through the devitalized intestinal wall of the isolated intestinal loop into the peritoneum, and from there being reabsorbed. When the ischemia was as advanced as that corresponding to the ligation of 15 mes end arc, only 5% of the dose leaked through the intestinal wall during the first 30 minutes after the intestinal damage was produced. Such an experimental group had, in the survival tests, an entirely necrotic intestinal loop 2-7 days after the ischemia was induced. Here, the vascular damage was moderate and corresponded to the ligation of only 7 mes end arc. This means a high degree of survival, and the surviving loop developed increased mural fibrosis (see Chapter VIII), which could be established histologically 7 and 14 days after the ischemic procedure. There could hardly be any possibility of leakage into the peritoneum, and I have abstained from closer analysis of this.

It was of greater interest to investigate the permeability of the intestinal wall to iodide *in vitro* under different experimental conditions.

Thus, *intervals of 7 and 14 days increase the primary inhibition of absorption that occurs after the ligation of 7 mes end arc; probably through secondary fibrosis of the mural layers of the intestinal loop.*

Chapter V. Permeability to NaI^{131} of the Ischemic Small Intestine

In Vitro

MATERIAL AND METHODS

The material consisted of 49 rats divided into 3 experimental groups. In group LC-7 days the animals had been laparotomized, and the previously defined loop of the small intestine had been indicated with threads 7 days prior to the experiment. In the groups 7 mes end arc-7 and 14 days, the experimental procedures (ligation and indication of the central loop) were performed 7 and 14 days before the recordings. Table III shows the experimental groups. For comparison, the group of intact controls (IC) from the earlier investigation (Nylander & Wikström, 1968) is included. The number of animals, and the means with s.e. for body weight and wet weight of the intestinal loop are given.

The animals were killed with ether. The intestinal loop was isolated by ligation from intestinal continuity and mesenteric connection. The measured dose of radio-iodide was deposited in the loop, after which this was excised and transferred to a beaker containing physiologic Krebs-Ringer solution. This was composed as follows per liter: 147 mEq of Na, 4.6 mEq of Ca, 4 mEq of K, and 160 mEq of Cl. It was thermostated at 37°C. The radioactivity of the loop was measured at the onset, and the result gave the initial value. After 15 minutes the loop was transferred to another beaker with an identical salt environment, and the radioactivity was again recorded. The difference between the counts was expressed in per cent of the initial value. The procedure was

repeated every 15 minutes, so that at the last recording the loop had been kept *in vitro* for 120 minutes. Glass beakers of a standard type were used. Their capacity was 25 ml. The amount of physiologic saline solution in each beaker for every investigation was 10 ml. The radioactivity was recorded during 2-minute periods and no fewer than 10,000 impulses were counted. The distance between the investigating table and the collimator (type PW-4113) was constant (15 cm).

RESULTS

Loss of radio-iodide from the intestinal loop was thus expressed in per cent of the original dose. Table IV shows the results as mean values with s.e. for all the experimental groups and experimental periods. Group IC was included for comparison. See also Fig. 1.

Group LC-7 days and group 7 mes end arc 7 days showed practically identical losses from the loop for all the recordings. After 120 minutes, in both these groups and in the IC-group the isolated loop had lost about 90% of the dose. After 15 minutes and 30 minutes the IC-group showed less loss, but for the further recordings the losses were of about the same order of magnitude as those of the two groups first mentioned.

After 15 minutes group 7 mes end arc-14 days had the same loss of iodide from the loop as that of the IC group. Thus, it was substantially lower than in group LC-7 days and group

TABLE III. *Characteristics of the material*

Experimental group	<i>n</i>	Weight (g)		
		Body		Isol. loop
		Initial	Final	
I C	11	206 ± 3.0		0.7 ± 0.02
L C	7 days	220 ± 1.9	200 ± 4.5	0.7 ± 0.03
7 mes end arc	7 days	231 ± 6.4	218 ± 5.4	0.9 ± 0.02
7 mes end arc	14 days	231 ± 5.6	246 ± 6.9	0.9 ± 0.05

TABLE IV. *In vitro* experiments. Transmural leakage of NaI^{131} from the isolated intestinal loop in different experimental conditions. The values are given in per cent of the radioactive dose. Mean values with S.E.

Experimental group	Experimental period in min.							
	15	30	45	60	75	90	105	120
I C	14±1.3	33±2.6	50±2.8	63±3.1	74±3.2	81±2.6	86±2.4	89±2.2
L C	22±3.1	41±3.8	55±4.5	66±4.4	76±3.8	82±3.2	86±2.9	89±2.6
7 mes end arc	26±3.0	44±3.8	59±3.6	70±3.2	78±2.8	84±2.3	88±1.9	91±1.6
7 mes end arc	13±1.6	26±3.2	38±4.2	49±5.2	58±5.6	64±5.6	70±5.4	74±5.4

7 mes end arc-7 days (Table IV). In the further course group 7 mes end arc-14 days showed, in all the recordings, significantly lower losses of iodide from the loop than did the other groups (Fig. 1). After 120 minutes the loss of radio-iodide from the isolated loop in group 7 mes end arc-14 days was 74%.

DISCUSSION

The radio-iodide deposited in the intestinal loop was allowed to pass through the intestinal wall into the physiologic saline solution for 120 minutes. The composition of both the iodide solution and the physiologic saline solution was defined

and constant. Thus, the fall in concentration of the iodide from the loop to the external solution was, from the outset, always the same and maximal. By renewing the external environment every 15 minutes the greatest possible concentration gradient was obtained over the membranous system, which the intestinal wall constitutes, until nearly the entire dose had left the intestinal specimen. Hence the difference in iodide leakage between the groups could be due only to such changes in the permeability of the intestinal wall to iodide as were caused by the severity and duration of the experimental condition.

Laparotomy performed only 30 minutes prior to an experiment of this kind reduced the passage

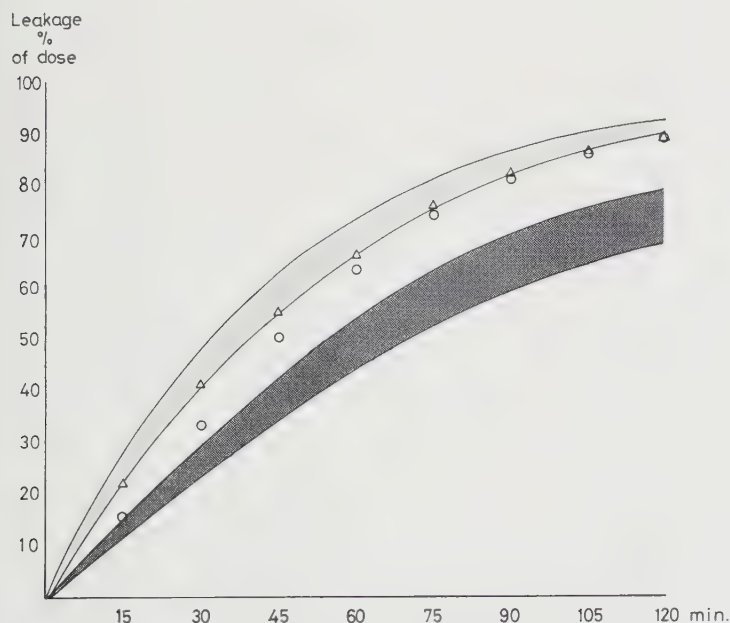


Fig. 1. The permeability to NaI^{131} *in vitro* of the surgically ischemic loop (7 mes end arc)—7 and 14 days after induction of ischemia. Leakage is expressed in per cent of the radioactive dose (vertical axis) and plotted against the experimental

period in minutes (horizontal axis). For the ischemic groups range areas are indicated. $\circ$, I C; $\triangle$, L C—7 days. Light shaded area: 7 mes end arc—7 days. Dark shaded area: 7 mes end arc—14 days.

of iodide through the intestinal wall (Nylander & Wikström, 1968). This condition was further accentuated if the time interval between the laparotomy and the analysis was prolonged (24 hours). The intestinal wall had become more impermeable to the water-soluble iodide. This was regarded as caused by fibrin precipitation on the surface of the intestine as part of an inflammatory reaction.

Surgically induced ischemia of the intestinal loop increased its permeability to iodide. This increase was most pronounced when there was a maximal degree of ischemia (15 mes end arc) that had persisted for a long time (24 hours). Thus, during the first 24 hours the surgically induced ischemia counteracted the decreased permeability due to laparotomy, and resulted in an increase in iodide leakage through the devitalized intestinal wall.

In this experimental series, after 7 days the leakage of radio-iodide through the intestinal wall was identical for the LC group and the 7 mes end arc group, and this leakage corresponded to a great extent with that for the IC group. As mentioned above reduction in permeability of the intestinal wall, resulting from laparotomy performed 24 hours previously, was assumed to be due to the exudation and precipitation of fibrin that forms part of the inflammatory reaction (Nylander & Wikström, 1968). The fact that the leakage after 7 days was nearly identical with that of the intact controls may indicate that this factor in the inflammatory reaction was then eliminated, so that the permeability of the intestinal wall to iodide was normalized. The surgically induced ischemia, which gave rise to increased leakage through the intestinal loop 24 hours after the operation (Nylander & Wikström, 1968), had 7 days later decreased the leakage so that it corresponded approximately with that of the intact controls.

After another week, *i.e.* 14 days after induction of ischemia, these animals showed, at every investigation, a substantially smaller leakage of radio-iodide from the loop. The ischemic damage had by this time caused the development of such changes in the intestinal wall that the transfer of iodide was decelerated. This condition is in good agreement with the results of the histological investigations which showed pronounced fibrosis in the intestinal wall (see Chapter VIII).

Chapter VI. Propulsive Gastrointestinal Motility

MATERIAL

In this part of the investigation a report is given on a total of 577 rats. The material was divided into 3 main groups, which, in accordance with the previous definitions, were designated 7 and 11 mes end arc respectively. A control group was included where only laparotomy was performed, including exploration of the intestinal loop which was devascularized in the other groups. As earlier, this group was called the LC group.

In addition to these groups, a group of intact control animals (IC) was also employed, which was reported on earlier in this respect (Derblom, Johansson & Nylander, 1966; Nylander & Wikström, 1968).

The experimental groups were divided according to the interval between the surgical procedure and the analysis of the propulsive motility. For the 7 and the 11 mes end arc groups this pre-experimental interval was 1, 3, 7, and 14 days, and for the LC group 1, 3, and 7 days. All the subgroups were in turn divided with regard to the duration of the experimental period (the interval between the deposition of the test dose into the stomach, and the time of analysis). Tables X-XII give the disposition of the material and the number of animals in each group and subgroup. Table VI presents the mean values for body weight in the different experimental groups. By initial weight is meant the weight of an animal when the laparotomy or the operation inducing ischemia was performed; and by final weight is meant the animal's weight at the time of the analysis.

METHODS

Propulsive gastrointestinal motility was recorded by the same method as was used in the earlier study (Nylander & Wikström, 1968). The method has been previously applied in several investigations dealing with problems of surgical interest (Johansson, 1966; Nylander & Wikström, 1967;

Nylander, 1967; Johansson & Nylander, 1968, etc.). As previously (Nylander & Wikström, 1968), the results were analyzed mathematically, in which connection the propulsive activity in different parts of the small intestine was evaluated in relation to the gastric emptying and the propulsion in general of the small intestine (Grevsten, Johansson & Nylander, 1967).

In principle, the method consisted in depositing a test meal including a radioactive substance in the stomach. The quantitative distribution of radioactivity in the gastrointestinal tract was subsequently recorded at different times. For a number of reasons radioactive chromate ($\text{Cr}^{51}\text{O}_4\text{Na}_2$) was held to be a suitable test substance.

The volume of the test meal was always constant and amounted to 1 ml. After the end of the experimental period the animal was killed with ether, the abdomen opened and the stomach isolated by ligation at the pylorus and cardia; after which the stomach, small intestine and caecum were removed, while retaining continuity. The gastrointestinal specimen was stretched out on a plexiglass plate, with the stomach at one end and the caecum at the other. By means of a colour indicator, which was always included in the test meal, it was possible to ensure that the distribution of the dose in the specimen had not been altered.

The quantitative distribution of the radioactive dose in the gastrointestinal specimen was recorded. This was done by passing the plate with the specimen under the tip of a scintillation detector at a speed that was synchronous with that of an automatic linear recording unit. A graphic representation was thus obtained, where the portion representing the stomach could readily be identified. The part representing the small intestine was divided into 10 consecutive and equal fractions.

The components of the graphic recording were evaluated planimetrically. The values for the stomach and the fractions of the small intestine were expressed in per cent of the planimetric



Fig. 2. Reaction of small intestine to regional ischemia 14 days after its surgical induction. (a) Type I. (b) Type II. (c) Type III (see text.).

value of the entire graph, corresponding to the total dose.

In an earlier series of experiments Nylander & Wikström (1968) showed that there was good agreement between the planimetric calculation and the direct counting over the stomach and small intestine. In this investigation, direct counting was omitted in respect of the stomach and small intestine. On the other hand, the method of direct counting over the colon was applied for the experimental periods of 60 and 120 minutes, in order to establish that the test dose, in its entirety, remained in the gastrointestinal specimen.

The method has been discussed in a number of previous papers (Derblom, Johansson & Nylander, 1966; Grevsten, Johansson & Nylander, 1967; Nylander & Wikström, 1968, etc.). It is sufficient to emphasize that the method measures only the *net effect* of the propulsive motility, *i.e.* the sum of such motor activity in the intestine as contributes towards the propulsion of the contents distally.

RESULTS

Appearance of the Gastrointestinal Specimen

In order to investigate the relation between the extent of the ischemia produced and the survival of the animals, the following experiments were carried out. In one group, consisting of 10 rats, 15 mes end arc were ligated. All the rats died within 7 days. The cause was invariably intestinal gangrene in the ischemic area. In another group, also consisting of 10 rats, the ligation was restricted to 7 mes end arc. In this group all the animals were still alive after 7 days.

In the following the propulsive gastrointestinal motility will be reported for cases with moderate ischemia, *i.e.* that produced by ligation of 7 mes end arc, with a resulting high survival rate. In addition to this, the corresponding functions will be reported for cases with more extensive ischemia, *i.e.* when 11 mes end arc were ligated. The survival rate during the first 14 days after the ischemic procedure will then probably be much lower.

TABLE V. The percentile distribution of living and dead animals into 3 different types

The number of animals is given in brackets. (See text)

Experimental group		Alive Type			Dead Type		
		1	2	3	1	2	3
7 mes end arc	1 day	100 (41)					
	3 days	100 (46)					
	7 days	85 (50)	9 (5)	3 (2)			3 (2)
	14 days	86 (54)	9 (6)	2 (1)			3 (2)
11 mes end arc	1 day	95 (40)			5 (2)		
	3 days	86 (44)	12 (6)				2 (1)
	7 days	49 (48)	11 (11)	11 (11)	2 (2)	3 (3)	24 (23)
	14 days	58 (55)	10 (9)	4 (4)	2 (2)	5 (5)	21 (20)

Surgical ischemia was found to produce changes in the intestinal wall that varied in a characteristic manner with regard to the macroscopic appearance. For this reason it was necessary to divide the material into 3 different types. The basis for such a classification was the macroscopic appearance of the ischemic area at the time of analysis. The different types were defined as follows.

Type I. The intestine seemed to be entirely intact within the ischemic area, apart from a moderate thickening.

Type II. In the corresponding area the intestine was considerably thickened for a short or long distance. The width above and below the enlarged section was normal.

Type III. Within the ischemic portion the intestine was more or less thickened, as in type II. Proximal to the swelling, however, the intestine was dilated, indicating an intestinal obstruction in the ischemic section (see also Fig. 2).

Table V shows the distribution of the animals in the various groups into these three types, in per cent of the total number of animals in each group; both surviving and dead animals are included.

It was found that all the animals in the 7 mes end arc group belonged to type I during the first 3 days following the induction of ischemia. After 7 and 14 days respectively, there was a moderate change to types II and III, and in both cases about 85% were regarded as belonging to type I. When ischemia was more pronounced, as in group 11 mes end arc, an increase in the change to types II and III was observed. After 3 days 86%, after

7 days 49%, and after 14 days 58% were considered to belong to type I.

Analytical results for the gastrointestinal propulsive motility are reported in the present work only for type I, as the statistical analysis of types II and III was regarded as unsatisfactory on account of the few animals which represented these types.

Mortality

From Fig. 3 it is evident that the mortality increased with the number of mes end arc ligated. Thus, in group 7 mes end arc the mortality after both 7 and 14 days was 3%, whereas in group 11 mes end arc it was, nearly 30% for the corresponding times. Fig. 4 shows the percentage distribution of the material according to the various types, and the mortality (shaded) in the groups 7 and 11 mes end arc, 7 and 14 days after the induction of ischemia. It is further apparent that in the group 7 mes end arc, death

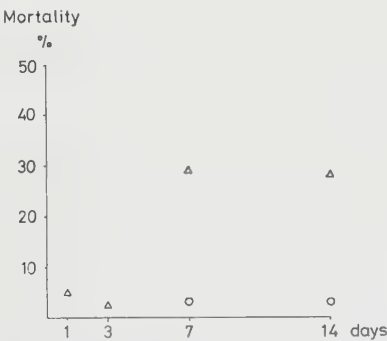


Fig. 3. Mortality rate in the ischemic groups plotted against duration of ischemia. ○, 7 mes end arc; △, 11 mes end arc.

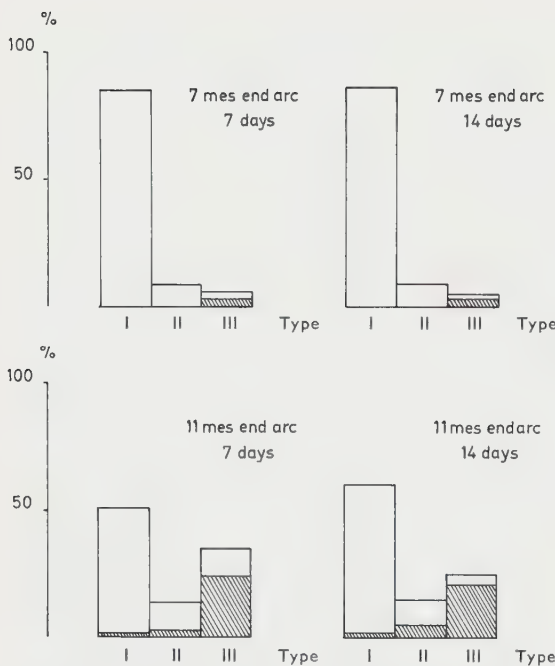


Fig. 4. Percentile distribution of the defined types of intestinal reaction to ischemia (I-III). Mortality is indicated by shaded area (see text).

occurred only with type III (pronounced intestinal obstruction) 7 and 14 days following the induction of ischemia. It is, moreover, evident that in group 11 mes end arc, death occurred mainly in type III 7 and 14 days after intervention. In type II the cause of death was considered to be intestinal perforation in the ischemic section of the intestine, with peritonitis. In group 11 mes end arc death occurred after massive intestinal bleeding in type I, 1, 7 and 14 days after the surgical ischemia.

Body Weight

In Table VI the mean values for body weight in groups LC, 7 and 11 mes end arc are presented, with the standard errors. The initial and final weight, as well as the changes of weight in grams are given for all the groups, except for the subgroups 1 and 3 days of the LC group. (This material has been included from a previous investigation by Nylander & Svensson, 1968.)

It is evident that in the LC-group the weight was the same after 7 days as when laparotomy was performed. Furthermore, in groups 7 and 11 mes end arc there was a reduction in weight during the first 7 days after ischemia was induced. On the other hand, after 14 days the mean weight had increased in both these groups.

Weight of Stomach and Small Intestine

The mean values, with standard errors, for the weight of the stomach are presented in Tables VII-IX for all the experimental groups and periods. In the LC group (Table VII) the weight possibly showed a tendency to decrease with increasing experimental time. The same tendency was observed in groups 7 and 11 mes end arc (Tables VIII and IX) with regard to the subgroups 7 and 14 days, whereas, the opposite tendency was noted for the subgroups 1 and 3 days.

Change in the weight of the stomach with an increasing experimental time can, under certain conditions, give a rough idea of the course of gastric emptying. Since, however, the amount of gastric secretion is not known, it is not possible to draw valid conclusions concerning the gastric emptying by only recording the weight—especially under varying experimental conditions.

Hence, the weight of the stomach does not af-

TABLE VI. Body weight (g) in the different experimental groups. Mean values with S.E.

Pre-exp. interval in days	Experimental group								
	L C			7 mes end arc			11 mes end arc		
	Initial	Final	Changes in weight (g)	Initial	Final	Changes in weight (g)	Initial	Final	Changes in weight (g)
1	214±2.6	—	—	225±2.0	217±1.6	-8±0.6	220±2.3	212±2.2	-8±0.7
3	204±1.9	—	—	221±1.2	212±1.5	-9±1.2	218±2.3	201±2.4	-17±1.9
7	212±1.6	212±2.1	0	226±2.3	224±2.3	-2±1.3	225±2.2	218±2.9	-7±2.3
14	—	—	—	221±3.1	244±2.8	+23±2.1	223±1.2	244±3.1	+21±3.1

TABLE VII. *Weight (g) of stomach and small intestine in the LC group. Mean values with S.E.*

Specimen	Experimental period in min.							
	30			60			120	
	Pre-exp. interval in days							
	1	3	7	1	3	7	1	3
Stomach	2.6±0.12	3.4±0.52	2.3±0.09	2.3±0.11	2.1±0.10	2.3±0.08	2.0±0.02	2.0±0.07
Intestine	—	—	10.5±0.28	—	—	10.5±0.23	11.2±0.44	10.6±0.40

TABLE VIII. *Weight (g) of stomach and small intestine in the 7 mes end arc group. Mean values with S.E.*

Specimen	Experimental period in min.							
	30			60			120	
	Pre-exp. interval in days							
	7	14	1	3	7	14	1	3
Stomach	2.4±0.10	2.6±0.09	1.9±0.11	1.8±0.10	2.1±0.08	2.1±0.08	2.0±0.14	2.0±0.08
Intestine	11.6±0.25	11.9±0.29	10.9±0.20	11.7±0.27	11.4±0.29	11.6±0.38	11.2±0.48	11.2±0.26

TABLE IX. *Weight (g) of stomach and small intestine in the 11 mes end arc group. Mean values with S.E.*

Specimen	Experimental period in min.							
	30			60			120	
	Pre-exp. interval in days							
	7	14	1	3	7	14	1	3
Stomach	2.2±0.10	2.6±0.08	1.7±0.10	1.7±0.08	1.9±0.11	2.2±0.12	2.3±0.12	2.2±0.09
Intestine	12.0±0.51	12.8±0.33	11.9±0.77	12.0±0.31	12.8±0.34	12.3±0.45	12.7±0.46	12.2±0.52

ford any indication of gastric emptying in either the laparotomized control material or in the actual experimental groups.

The weight of the intestine (Tables VII-IX) is increased when the degree of ischemia is more pronounced. This can probably be explained by the reaction of the intestinal wall to the ischemia. Initially, bleeding, oedema, infiltration etc. occur, and subsequently, where the healing process takes place, there is more or less pronounced fibrosis of the intestinal wall.

Gastric Emptying

The quantitative distribution of the radioactive dose in the stomach and small intestine is shown in Tables X, XI, and XII for groups LC, 7 mes

end arc, and 11 mes end arc with their subgroups and respective experimental periods. The results are expressed as mean values with standard errors. Fig. 5 gives a graphic illustration of the gastric emptying in all the experimental groups. Mean values for radioactivity retained in the stomach are plotted against experimental time.

An intact control material (IC) was included for comparison. It has been reported on previously (Nylander & Wikström, 1968).

It is shown that in the IC group gastric emptying had an initially rapid, and subsequently retarded course. After 15 minutes the stomach contained about 45% of the dose, after 30 minutes less than 30%, and after 60 minutes less than 20%.

Earlier, Nylander & Wikström (1968) showed that in the LC group, in immediate connection

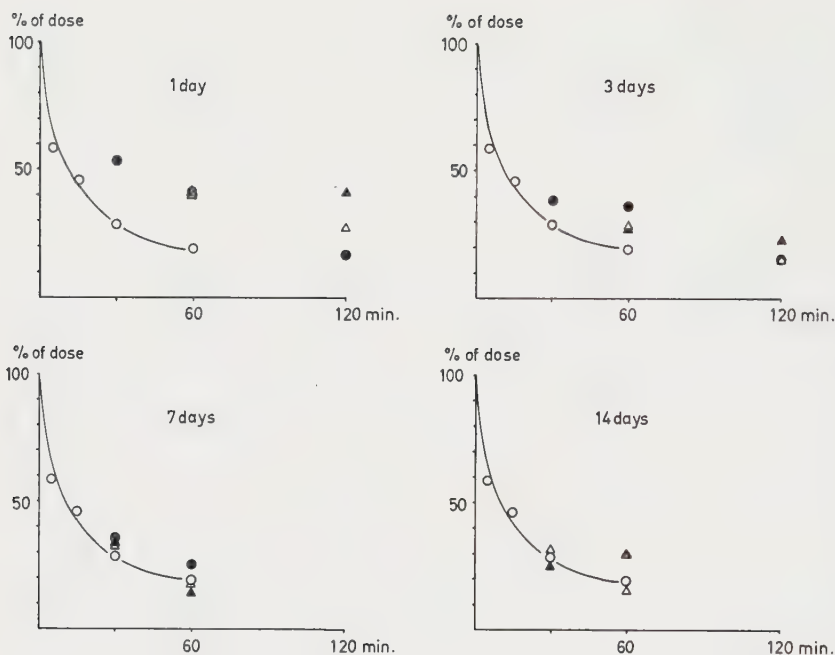


Fig. 5. Course of gastric emptying in all the experimental groups 1–14 days after induction of ischemia. The radioactivity remaining in the stomach is expressed in per cent of the dose and plotted on the vertical axis against experimental period on the horizontal axis. ○, IC; ●, LC; △, 7 mes end arc; ▲, 11 mes end arc.

with laparotomy, 70% of the dose was retained in the stomach after 1 hour, and 35% after 2 hours. When the LC group was analyzed 24 hours after laparotomy, the stomach contained about 40% of the dose after 1 hour, and after 2 hours less than 20%. Analysis 3 and 7 days after laparotomy, showed that the part of the test dose which then remained in the stomach decreased successively. In the latter case the degree of gastric emptying was essentially the same as that in the IC group after both 30 and 60 minutes.

In immediate connection with induction of ischemia the group 7 mes end arc had a gastric retention of hardly 50% of the dose after 1 hour, and about 25% after 2 hours (Nylander & Wikström, 1968). Fig. 5 shows that when analysis was made 24 hours after induction of ischemia, about 40% was retained after 1 hour and less than 30% after 2 hours, in other words the degree of gastric emptying was, at these experimental times, approximately the same. On analysis after 3, 7, and 14 days gastric emptying was successively normalized, so that after both 7 and 14 days it corresponded to that of the IC group for the same experimental periods.

Similarly, in group 11 mes end arc, immediately after induction of the ischemia about 65% of the dose was retained in the stomach after 1 hour, and just over 50% in 2 hours (Nylander &

Wikström, 1968). Twenty-four hours after the procedure, about 40% of the dose was retained after 1 hour, and the same value was obtained after 2 hours. On analysis after 3, 7, and 14 days as in the groups LC and 7 mes end arc, the gastric retention at the given experimental times decreased successively. On analysis 7 days after the induction of ischemia the gastric emptying was nearly identical with that in both the groups 7 mes end arc and LC. Fourteen days after induction of the ischemia a somewhat larger part of the dose was retained in the stomach after 60 minutes in the group 11 mes end arc than in any of the other groups.

Discussion

The intact control material has been taken from an earlier investigation (Derblom, Johansson & Nylander, 1966). In another study (Nylander & Wikström, 1968), where the same intact control material was used, it was presumed that emptying after 1 hour might be somewhat more pronounced than that reported (19%). Values between 10% and 15% were given by Johansson (1966) and Johansson & Nylander (1967).

By comparing the gastrointestinal motility functions in intact and in laparotomized animals it was possible to assess the isolated effect of laparotomy. On the basis of these results it was subse-

quently possible to determine the effect that ischemia of an intestinal loop could have on the motility functions in question.

Laparotomy, including exploration of the small intestine causes, as we have previously shown (Nylander & Wikström, 1968) pronounced retardation of gastric emptying. This effect persists for not less than 3 days, when the function is still moderately delayed (Nylander & Svensson, 1968).

From my results it is evident that the substantial retardation of the gastric emptying that was obtained in immediate connection with the operation, decreased successively with time. Fig. 5 illustrates that this was already the case after 24 hours, and that after 7 days there was either only slight, or no retardation at all of gastric emptying in the laparotomized animals compared with the intact animals. The inflammatory reaction, which it is assumed that laparotomy produces, and which might be the cause of both reduction in gastric emptying rate and permeability to radio-iodide *in vitro*, can be assumed to have decreased after 7 days.

Propulsive gastrointestinal motility was analyzed in the experimental groups where 7 and 11 mes end arc were ligated. Our previous investigation showed (Nylander & Wikström, 1968) that gastric emptying in the group 7 mes end arc was initially more rapid than in the LC group when analysis was made in immediate connection with the procedure. The rapid initial phase in group 7 mes end arc lasted 1–2 hours. If surgical ischemia was more pronounced and covered the ligation of 11 mes end arc, the effect on the gastric emptying was, on the contrary, inhibitive, especially during the experimental period of 1–2 hours. In view of these observations the following hypothesis may be advanced. Motor activity in one part of the gastrointestinal tract can cause a corresponding condition in other parts of the system, what are known as intestinal reflexes (Davenport, 1966). A condition of moderate anoxemia in the smooth muscle layers of the ischemic intestine might locally activate motility and, via some receptor mechanism, release such a reflex as activates the emptying of the stomach. Such moderate anoxemia is the result of the ligation of 7 mes end arc. When devascularization is more extensive—the ligation of 11 mes end arc—and anoxemia is increased in the intestinal wall, the hypothetical receptor

mechanism might be destroyed or incapable of functioning. The emptying of the stomach was substantially retarded immediately after 11 mes end arc had been ligated. Nor is it possible to exclude that even now a long intestinal reflex is released from the paralyzed ischemic section of the intestine and producing a paralyzing effect on gastric motility (intestino-gastric reflex).

However, 24 hours after induction of the ischemia the gastric emptying had essentially recovered its normal function in the group 11 mes end arc. This means that the *retarding* effect on gastric emptying had been eliminated. In the group 7 mes end arc normalization had also occurred, in other words the primary *accelerative* effect on emptying had ceased. Thus, after 1 hour the emptying of the stomach was about 40% in all the groups.

On the basis of the previous discussion the course of gastric emptying in the different groups after 24 hours may possibly be explained in the following way. A receptor mechanism in the smooth muscle layers or neuromuscular structures in the ischemic section of the intestine might produce, in the case of moderate anoxemia (7 mes end arc), an accelerative effect on gastric emptying. When there is a higher degree of anoxemia (11 mes end arc), this mechanism might be prevented from functioning and another paralyzing effect on the motility of the stomach is introduced. Twenty-four hours after the induction of the ischemia, oxygenation had improved through increased utilization of collateral systems; and the differences that existed in gastric emptying after 120 minutes can probably be explained by the different degrees of anoxemia which still persisted in the ischemic section in the different groups.

Subsequently, the emptying of the stomach was increasingly normalized, and after 7 days it was practically identical with that of intact controls.

After 14 days, however, the most devascularized group (11 mes end arc) showed a tendency towards retarded emptying of the stomach after 1 hour, in relation to the other groups. This may have been a late consequence of the effect of the ischemia on the intestinal wall, *i.e.* increased fibrosis and a tendency to stenosis. This condition will be analyzed further in connection with the evaluation of the propulsive motility in the small intestine.

TABLE X. *L C*. Percentile distribution of the radioactive dose in the stomach and small intestinal fractions in different experimental conditions. Mean values with S.E.

Specimen	Experimental period in min.							
	30			60			120	
	Pre-exp. interval in days							
	1	3	7	1	3	7	1	3
Stomach Fraction	54±6.5	38±5.7	35±3.6	41±6.0	37±4.9	25±3.1	17±2.6	16±3.5
1	3±0.8	4±0.4	4±0.3	3±0.4	3±0.3	3±0.4	3±0.2	2±0.4
2	4±1.0	5±0.5	6±0.8	4±1.0	4±0.8	4±0.7	3±0.5	3±0.5
3	5±1.0	7±0.7	10±1.4	6±1.4	7±1.4	5±0.9	4±0.7	4±0.6
4	5±1.0	9±1.0	13±1.6	8±1.7	6±1.1	12±1.6	10±1.9	7±1.2
5	7±1.2	10±1.4	13±1.4	8±2.0	10±2.3	18±2.0	13±2.4	11±2.1
6	7±1.6	9±1.4	10±1.2	9±1.8	12±1.8	18±2.2	13±2.3	16±2.6
7	6±1.2	7±1.2	6±1.0	10±2.1	11±1.7	10±2.0	12±2.3	12±2.4
8	5±1.0	6±1.1		8±1.6	6±2.1		14±3.0	8±2.2
9							10±2.8	13±3.5
10								7±3.5
n	15	15	21	15	15	21	20	20

Propulsive Motility in the Small Intestine

The percentage distribution of the test dose in the consecutive and equal fractions of the small intestine is given in Tables X-XII for all the groups and experimental periods. The results were obtained by planimetric determination of the graphical recordings, and are given as mean values with standard errors. All values less than 5% of the dose and representing fractions in close approximation to the propulsive front are excluded.

The results are presented as histograms in Figs. 6-17. They comprise two series. The first series shows the distribution of the test dose in each of the three main groups at the same experimental periods. It is then possible to determine in these groups the redistribution of the dose as a function of the time that has elapsed between laparotomy or induction of the ischemia and the analysis. In order to obtain a basis for comparison, in this investigation some experimental groups from a previous study have been included (Nylander & Wikström, 1968). Thus, the presentation of the LC group has been complemented by the IC group. Similarly the LC, 7 and 11 mes end arc groups, which were analyzed in immediate connection with the respective procedures, have been included in their respective main groups. The three groups mentioned will be called in the following LC-0 day, 7 mes end arc-0 day and 11 mes end arc-0 day. Comparisons were made with

regard to the LC group on days 0-7, and in the ischemic groups 7 and 11 mes end arc, on days 0-14. The experimental periods were 30 and 60 minutes respectively.

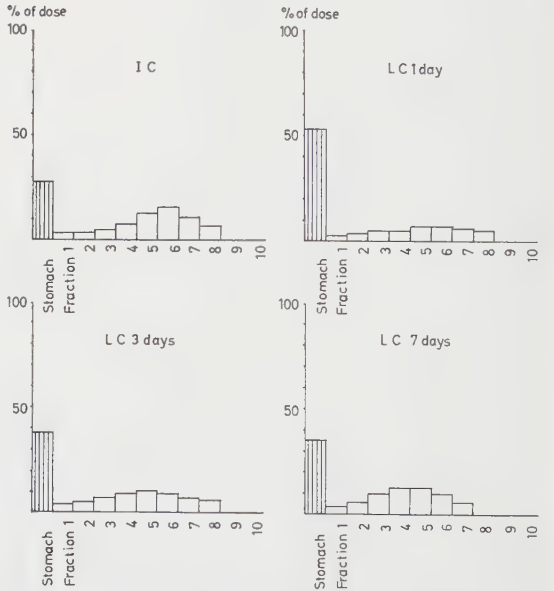


Fig. 6. Presentation according to series I. Histograms representing the IC group and the LC group 1-7 days after surgery. Experimental period 30 min. The radioactivity is given in per cent of the total dose on the vertical axis; for the stomach, indicated by vertically shaded rectangle, and for the 10 consecutive, equal-sized fractions of the small intestine by hollow rectangles.

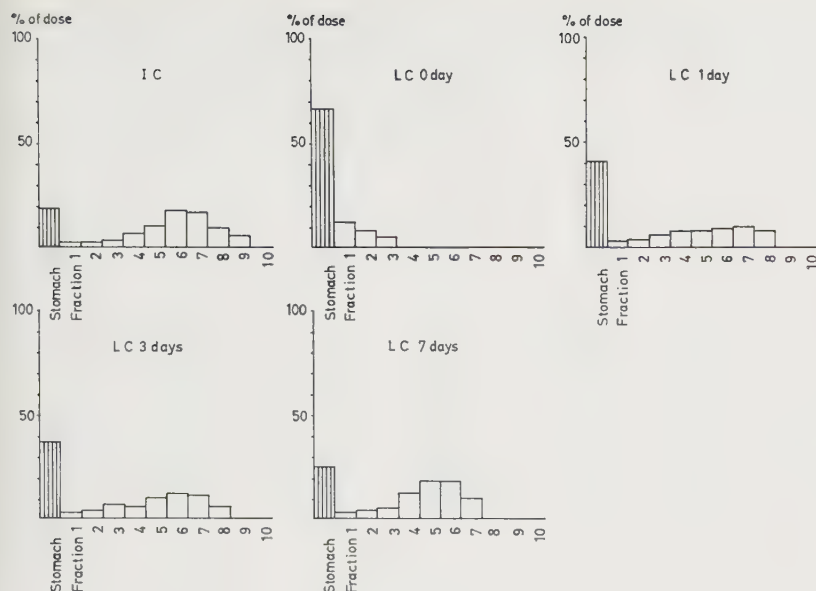


Fig. 7. Presentation according to series I. Histograms representing the IC group and the LC group 0-7 days after surgery. Experimental period 60 min.

In the second series the different main groups are compared in the same way on the same day after the respective procedures and for identical experimental periods. Also here the IC group from an earlier material has been included for comparison. Thus, this mode of presentation deals with the effect of the respective procedures without the postoperative time being varied.

(a) Presentation according to series I

In the LC-group, as shown in Table X and Fig. 6, after 30 minutes the subgroup LC-1 day had evacuated about 45% of the test dose into the small intestine. This portion was fairly evenly distributed in fractions 1-8.

In the subgroup LC-3 days, just over 60% had been evacuated into the small intestine. The portion was still dispersed over fractions 1-8. The distribution indicated a stepwise increase up to fraction 5.

When 65% of the dose was evacuated into the small intestine in subgroup LC-7 days, fractions 4 and 5 were the largest; and the stepwise distribution up to these was now more distinct.

Fig. 6 shows that with the lapse of time after laparotomy, there was an increased evacuation into the small intestine. A distinctive feature of the quantitative distribution was that the intermediate fractions 4-6 increased in size. After 7 days the propulsive pattern had assumed a cha-

racter suggesting similarity to that in the IC group.

Table X and Fig. 7 show, in a similar way, the LC group at 60 minutes. In subgroup LC-0 day, 35% of the test dose was evacuated into the small intestine. This whole portion was situated in the three proximal fractions. Fraction 1 was the largest and fraction 3 the smallest. In the next subgroup, LC-1 day, about 60% of the test dose had been evacuated and distributed between fractions 1-8. The distribution was comparatively even between fractions 4-8, and fraction 1 was the smallest. As the lapse of time after laparotomy increased a successively larger portion was evacuated into the small intestine, where the dose was accumulated especially in fractions 5 and 6. After 7 days, the propulsive pattern was nearly identical with that of the IC group.

Group 7 mes end arc with the subgroups 1-14 days are presented in Table XI for all the experimental periods, and in Fig. 8 at the experimental period of 60 minutes. The subgroup 7 mes end arc-0 days has been included as a reference in Fig. 8. From the latter it is evident that during 1 hour just over 50% of the dose had been evacuated in this group. The distribution was entirely restricted to the proximal half of the intestine; and its five fractions contained approximately equal parts of the dose.

On analysis 24 hours after induction of the

TABLE XI. 7 mes end arc. Percentile distribution of the radioactive dose in the stomach and small intestinal fractions in different experimental conditions. Mean values with S.E.

Specimen	Experimental period in min.							
	30				60			
	Pre-exp. interval in days							
	7	14	1	3	7	14	1	3
Stomach Fraction	32±3.4	31±2.8	40±3.9	28±3.1	18±2.7	15±2.8	27±4.6	15±3.1
1	3±0.4	3±0.5	3±0.4	2±0.4	2±0.3	1±0.3	3±0.8	1±0.3
2	4±0.5	5±0.9	6±1.0	3±0.6	2±0.5	2±0.4	3±0.6	1±0.5
3	8±1.2	6±0.7	9±1.4	4±0.8	3±0.6	3±0.5	3±0.4	3±1.1
4	12±1.3	10±0.8	11±1.6	7±1.3	3±0.6	6±0.9	5±1.5	4±1.1
5	14±1.2	16±1.1	11±2.1	15±2.3	8±1.4	15±2.4	8±2.2	6±1.3
6	12±1.5	12±1.1	9±1.9	14±2.4	20±2.8	20±2.2	9±1.8	10±1.9
7	10±1.3	9±1.2	6±1.9	13±2.5	22±2.4	18±2.1	12±1.8	14±1.8
8		6±1.0		7±1.3	14±2.2	13±2.8	16±2.9	15±2.4
9					7±1.5	5±1.4	12±2.8	22±4.3
10								9±2.5
n	24	29	20	22	26	25	21	24

ischemia, 60% of the dose was present in fractions 1-7. The distribution was in a more distal direction than when analysis was made immediately following induction of the ischemia. The size of the fractions was built up against fractions 4 and 5.

As the period of time after the intervention was prolonged, an increasingly large part of the dose was emptied into the small intestine, after 3 days about 70% (fractions 1-8), after 7 days about

80% (fractions 1-9), and after 14 days about 85% (fractions 1-9). Parallel with this, distribution of the evacuated dose became more and more distal; and fractions 6 and 7 were increasingly built up. Thus, 14 days after induction of the ischemia, the distribution in group 7 mes end arc was in close agreement with that of the IC group at the experimental period of 60 minutes (see also Fig. 17).

The subgroups representing group 11 mes end

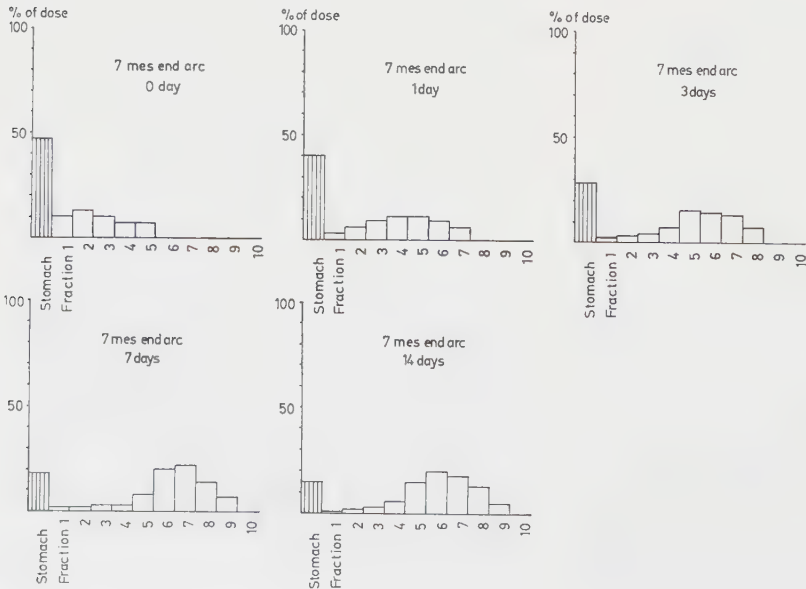


Fig. 8. Presentation according to series I. Histograms representing the group 7 mes end arc 0-14 days after surgery. Experimental period 60 min.

TABLE XII. *11 mes end arc*. Percentile distribution of the radioactive dose in the stomach and small intestinal fractions in different experimental conditions. Mean values with S.E.

	Experimental period in min.							
	30		60		120			
	Pre-exp. interval in days							
Specimen	7	14	1	3	7	14	1	3
Stomach Fraction	33±4.0	25±2.9	41±4.7	27±3.9	14±2.3	29±4.6	41±4.4	22±3.4
1	3±0.4	3±0.3	5±1.1	2±0.4	1±0.2	2±0.2	4±0.8	2±0.3
2	4±0.6	4±0.6	9±1.0	3±1.4	1±0.3	2±0.2	5±1.2	2±0.3
3	7±1.2	8±1.2	12±2.0	5±1.4	3±0.5	3±0.4	6±1.0	2±0.3
4	10±1.3	11±1.1	8±0.9	7±1.6	4±1.0	4±0.7	8±1.7	2±0.4
5	11±1.4	18±1.3	8±2.1	11±1.9	10±2.0	11±1.7	10±2.0	5±1.4
6	13±1.7	15±1.3	7±2.0	15±2.4	16±2.4	21±2.7	10±1.8	8±1.6
7	11±2.0	8±0.9		14±1.9	18±3.2	16±2.3	9±3.0	14±3.1
8	5±1.3			9±2.6	16±3.1	8±1.8		17±2.5
9				5±1.7	12±2.6			17±2.5
10								10±2.4
n	23	27	20	22	25	28	20	22

arc 1–14 days, and all their experimental periods are given in Table XII; as well as at the common experimental period of 60 minutes in Fig. 9. In this figure *11 mes end arc*-0 day has been included. In the latter group, during 60 minutes 35% of the dose was emptied into the small intestine and distributed between fractions 1–3, which were all about the same size. After 24 hours about 60% of the dose had been evacuated

from the stomach. This portion was recorded in the first 6 fractions. Fraction 3 was the largest. After 3 days the evacuated portion amounted to 70% of the dose. The distribution was now much more distal, and the front reached the 9th fraction. Fractions 6 and 7 were dominant, and the first two fractions were the smallest.

When, after 7 days about 85% of the dose had been emptied into the small intestine (fractions

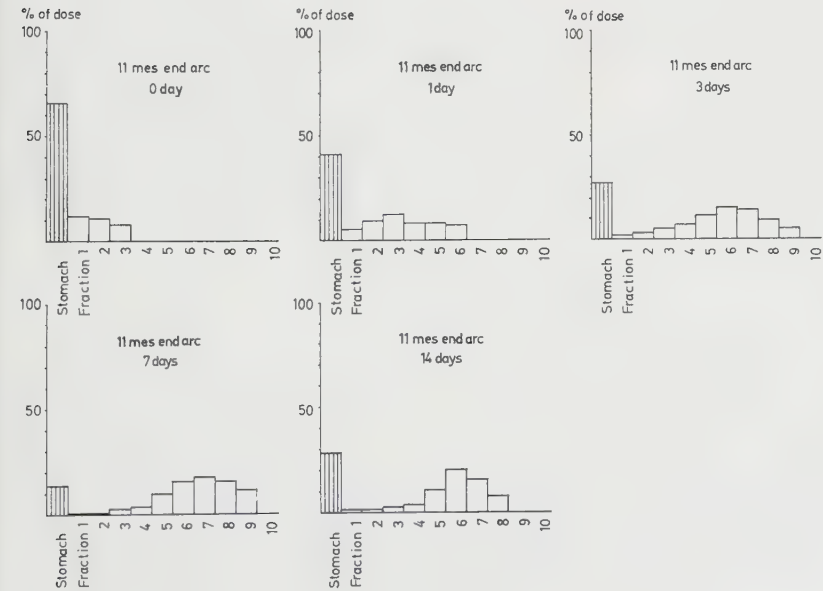


Fig. 9. Presentation according to series I. Histograms representing the group *11 mes end arc* 0–14 days after surgery. Experimental period 60 min.

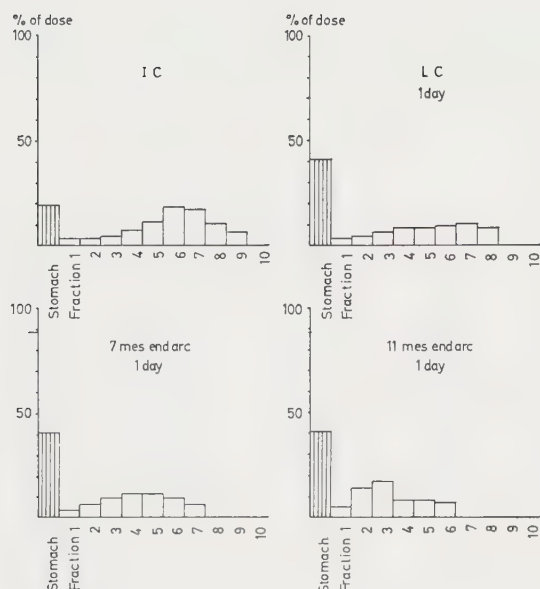


Fig. 10. Presentation according to series II. Histograms representing the IC group and the experimental groups 1 day after surgery. Experimental period 60 min.

1-9), the distribution had shifted still further distally. Fractions 6-8 were the largest and fractions 1-2 were insignificant.

This development was interrupted 14 days after induction of the ischemia, when about 70% of the dose had been emptied into the small intestine. The dose occupied the first 8 fractions. Fractions 6 and 7 dominated the histogram. Fractions 1 and 2 were still the smallest. Thus, after 14 days a smaller part of the dose was evacuated into the small intestine than after 7 days. This condition is worthy of note, and will be discussed later.

(b) Presentation according to series II

Duration of regional ischemia=1 day. Fig. 10 shows that in all the experimental groups about 60% of the test dose had been evacuated into the

small intestine after 60 minutes. The evacuated portion was distributed differently, however, in the three groups. In the LC group the distribution was fairly even in all the fractions, including fraction 9, which was the front fraction. Fractions 4-8 were approximately the same size. In group 7 mes end arc the corresponding distribution was rather more proximal in character. Fraction 7 formed the front. Fractions 3-6 were dominant and about equal in size. This tendency was still more accentuated in group 11 mes end arc. Here fraction 6 formed the front, and fractions 2 and 3 were dominant. As shown in Fig. 10, a substantially smaller part of the dose was evacuated in all the experimental groups than in the IC group. Apart from this, the propulsion pattern in the LC group was similar, in principle, to that of the IC group. In the ischemic groups, however, the propulsion pattern was shifted proximally; this was most pronounced in the group that had been subjected to the severest ischemia.

Fig. 11 shows a corresponding pattern after an experimental period of 2 hours. About 85% of the test dose had then been evacuated in the LC group, 75% in group 7 mes end arc, and in group 11 mes end arc there had been no further evacuation, but about 60% was still recorded in the intestine.

In all the three groups distribution of the dose was now more distal than after 1 hour. However, the radioactive front in the LC group was in the 9th fraction. The distribution between the fractions remained comparatively equal, but fraction 9 had increased its share of the dose, so that fractions 4-9 were the largest and approximately equal in size. In group 7 mes end arc the amount evacuated from the stomach was somewhat less, but the front of the evacuated portion extended as far as it did in the LC group, including the 9th

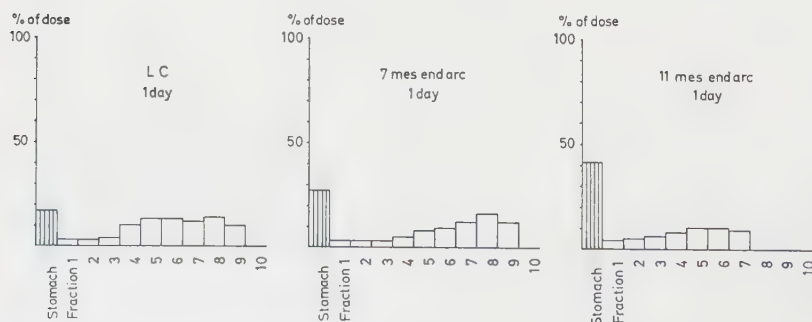


Fig. 11. Presentation according to series II. Histograms representing the experimental groups 1 day after surgery. Experimental period 120 min.

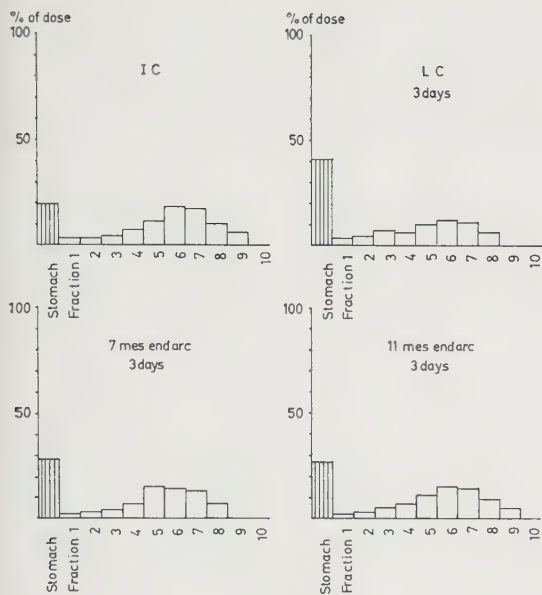


Fig. 12. Presentation according to series II. Histograms representing the IC group and the experimental groups 3 days after surgery. Experimental period 60 min.

fraction. The distribution of the dose was definitely more distal in this group. In group 11 mes end arc there was no further evacuation of the dose into the small intestine during the last hour. On the other hand, it had been redistributed in a distal direction, so that fractions 5-7 were now the largest and the same size.

Duration of regional ischemia=3 days. Fig. 12 shows that 3 days after laparotomy the LC group had evacuated just over 60% of the test dose after 60 minutes. At corresponding times groups 7 mes end arc and 11 mes end arc had emptied just over 70% into the small intestine. The evacuated portion was distributed, in all the groups, between the first 8-9 fractions. Of these, fractions 5-7 were the largest throughout, and were fairly equal in size in the various groups. The distribution was

more distal in group 11 mes end arc. When the experimental groups were compared with the IC group, then the latter had a much more effective evacuation. It was striking that the propulsion pattern, in the group subjected to the highest degree of ischemia, was developed furthest distally, and resembled, to a great extent, the pattern in the IC group.

As is shown in Fig. 13, after an experimental period of 2 hours about 85% of the test dose had been evacuated into the small intestine in both the LC group and the 7 mes end arc group, whereas the corresponding value for group 11 mes end arc was hardly 80%. The distribution of the dose covered, in all the groups, all the 10 fractions. In order to ensure that the entire test dose was present in the gastrointestinal preparation, the method of direct counting over the colon was

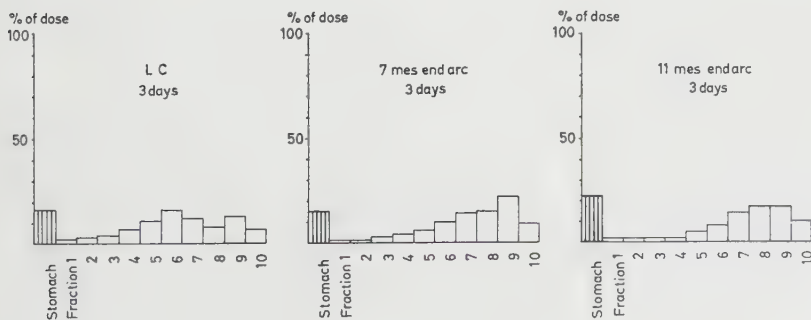


Fig. 13. Presentation according to series II. Histograms representing the experimental groups 3 days after surgery. Experimental period 120 min.

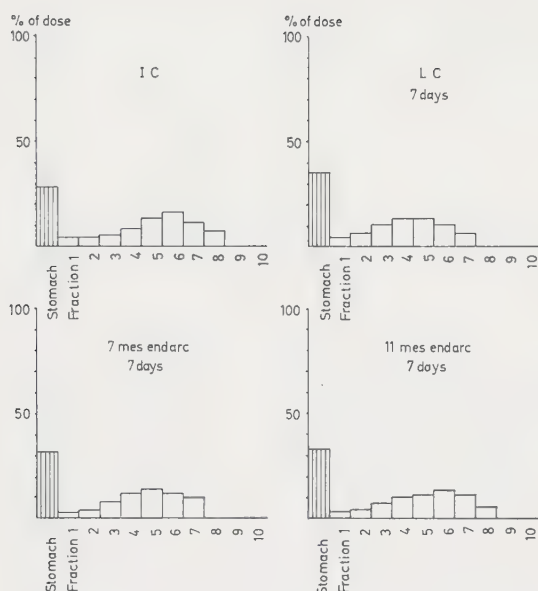


Fig. 14. Presentation according to series II. Histograms representing the IC group and the experimental groups 7 days after surgery. Experimental period 30 min.

applied in all the one- and two-hour experiments. In no case was any activity recorded that exceeded the background. All the groups had, during the hour that had elapsed, increased their distribution of the dose distally. In this series the dose seemed to be distributed more distally in both the ischemic groups than in the LC group. Thus, group 7 mes end arc had now also a more effective distal redistribution of the dose than the LC group.

Duration of regional ischemia=7 days. In the LC group 65% of the dose was distributed in the small intestine during an experimental period of 30 minutes (Fig. 14). In the groups 7 and 11 mes end arc about the same amount was recorded in the small intestine for the corresponding experimental period. The front was located in groups LC and 7 mes end arc in fraction 7, and in group 11 mes end arc in fraction 8. In the LC group the different fractions were quantitatively built up against fractions 4-5, which were the largest. In principle, the same applied to the group 7 mes end arc, where fractions 4-6 were the largest; whereas fractions 5-7 were dominant in the group 11 mes end arc. Thus, the distal distribution of the dose was most pronounced in this

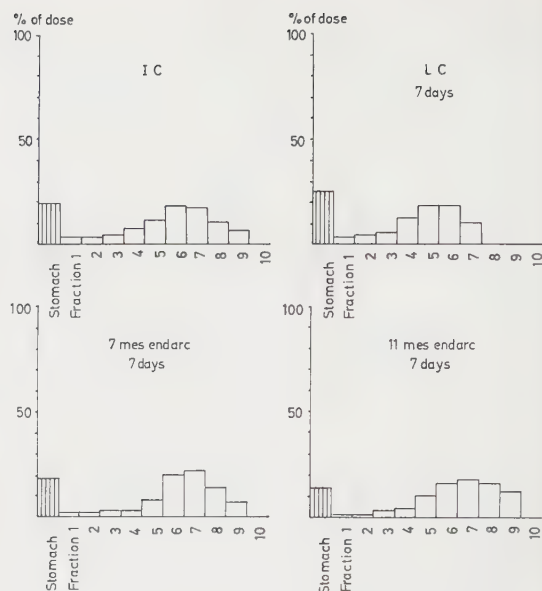


Fig. 15. Presentation according to series II. Histograms representing the IC group and the experimental groups 7 days after surgery. Experimental period 60 min.

group, the propulsion pattern of which showed close agreement with that of the IC group.

Fig. 15 illustrates the corresponding distribution after 60 minutes. The LC group had evacuated 75% of the test dose, and group 7 mes end arc about the same (slightly over 80%). Group 11 mes end arc was possibly more effective, and had emptied just over 85% during the same experimental period. The distal front of the dose was represented in the LC group by fraction 7 and, in both of the ischemic groups, by fraction 9. Moreover, in the LC group the dominant fractions (5 and 6) were situated more proximally than in the ischemic groups (6-7, and 6-8 respectively). During the last 30 minute period the gastric emptying was most effective in the group 11 mes end arc, where the distal distribution was also most pronounced and, essentially, the same as in the IC group.

Duration of regional ischemia=14 days. From Fig. 16 it is evident that both the ischemic groups had, after 30 minutes, emptied about the same portion of the dose into the small intestine. The values were about 70% in group 7 mes end arc, and about 75% in group 11 mes end arc. The distribution had also the same character. In group

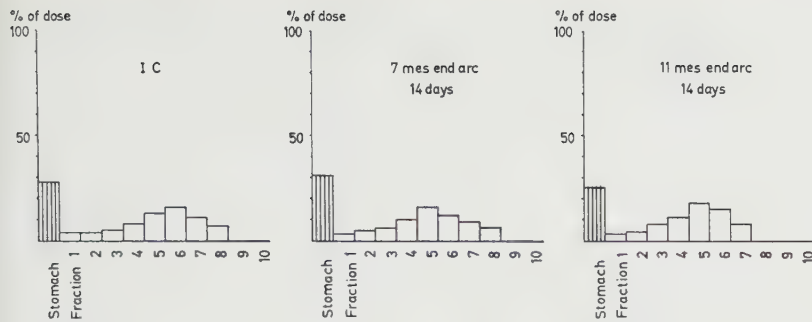


Fig. 16. Presentation according to series II. Histograms representing the IC group and the experimental groups 14 days after surgery. Experimental period 30 min.

7 mes end arc the front was situated in fraction 8; and in group 11 mes end arc in fraction 7. Fraction 5 was the largest in both groups. The intestinal distribution was, in principle, the same in both the ischemic groups and identical with that of the IC group.

Fig. 17 shows that about 85% of the test dose was present in the small intestine after 60 minutes in group 7 mes end arc, and just over 70% in group 11 mes end arc. In group 7 mes end arc the evacuated portion included fraction 9, and in group 11 mes end arc fraction 8. In both groups fraction 6 was the largest. Group 7 mes end arc still corresponded to the IC group with regard to distribution pattern, whereas group 11 mes end arc was retarded in respect to both the gastric emptying and the propagation of the dose.

DISCUSSION

Before discussing the distribution pattern of the radioactive substance in the small intestine, some factors should be elucidated that may be of importance for evaluating the results.

One such factor is the extent to which the distribution of the test dose in the gastrointestinal preparation is influenced by the free dissection of

the adhesions that occur in the abdomen and that appear especially after 7 and 14 days. On the basis of the macroscopic appearance of the ischemic section of the gut when the analyses were made, the experimental material was divided, as previously stated, into three types. Only animals belonging to type I were used for these motility analyses. In this material the formation of adhesions was insignificant, and of about the same extent as in the laparotomized control material. More manipulations are required to dissect out the gastrointestinal preparation when adhesions have first to be dissected free. The fasting animal's intestine, which is strongly contracted in connection with death, can, however, be handled with less care without any of its contents being displaced (Derblom, Johansson & Nylander, 1966). Furthermore, the same conditions held good for the laparotomized controls. Should, contrary to expectation, some slight change occur in the distribution of the test dose in the gastrointestinal preparation, this is probably insignificant and similar in all the groups; and may definitely be regarded as of no importance for the results.

Another factor which should be observed when assessing the results as presented in the histograms, is the comparatively wide scatter, with a

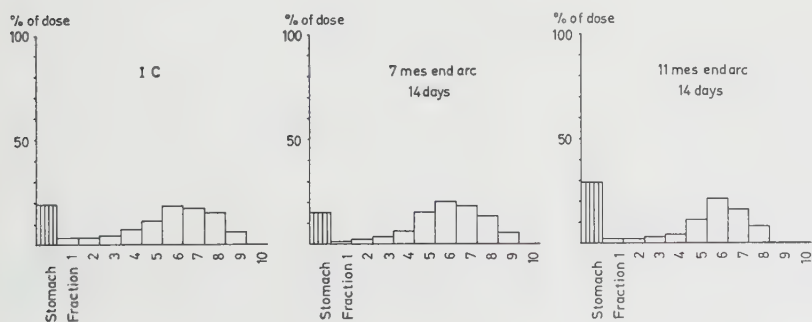


Fig. 17. Presentation according to series II. Histograms representing the IC group and the experimental groups 14 days after surgery. Experimental period 60 min.

standard error amounting to 10–20% of the analytical values (Tables X–XII). These individual differences between the animals, especially in the propagative function of the small intestine are thus due not to methodological, but to biological, causes, and occur despite standardization of all the experimental conditions.

The immediate effect of laparotomy was substantial delay in gastric emptying and insignificant propagation of the evacuated portion (Nylander & Wikström, 1968). After one day, the stomach had recovered something of its normal function and had emptied a large part of the test dose into the small intestine, where propulsive motility had also been recovered, and the contents had been distributed a long way distally. The longer the interval after laparotomy the more normalized the gastric emptying and the propulsive motility of the small intestine. This condition seems, in principle, to support the view that, if a sufficient amount of the gastric contents was supplied the intestine, its autonomous capacity was able to transport it a substantial distance along the intestine (Nylander & Wikström, 1968). In other words, the evacuative mechanism of the stomach was, in part, decisive for the effectiveness of the propulsive intestinal motility. In the intact control animals these two functions were nearly identical with regard to a large part of the small intestine (Grevsten, Johansson & Nylander, 1967). A mathematical analysis of the propagative function of the intestine subjected to ischemia (Chapter VII) showed, however, that the recovery of the function of gastric emptying was more rapid than that of small intestinal propulsion.

The emptying capacity of the stomach, immediately after laparotomy, was greatly reduced; and recovery was surprisingly slow. After 7 days, however, both gastric emptying and the propulsion in the small intestine corresponded almost entirely with the functions of the intact control animals. Thus, the effect of laparotomy on the gastrointestinal propulsive motility had almost completely disappeared after 7 days.

The two experimental groups, with different degrees of local intestinal ischemia, will be assessed on the basis of these observations, in order to isolate the effect of ischemia from the simultaneous influence that the requisite laparotomy had on the functions in question.

The relatively moderate, regional ischemia,

which is produced by the ligation of 7 mesenteric arc, caused, initially, acceleration of gastric emptying and more effective distal propagation of the intestinal contents. The condition has been analyzed previously, and was presumed to have been due to a long reflex from the ischemic loop of the small intestine to the stomach. Local factors in the ischemic segment (bleeding, stasis, oedema etc.) could be assumed to influence the hypothetical receptors in its neuromuscular system. In this way, moderate ischemia might cause accelerated gastric emptying. As a consequence of this, the distal distribution in the intestine would be more effective.

After ischemia had been allowed to persist for 24 hours, the gastric emptying was nearly normalized in respect to the ischemic effect; and the propagative function of the intestine was slowed down. This tendency, to inhibition of the propulsive motility functions 24 hours after a moderate degree of ischemia had been induced, can probably also be accounted for by local changes which can then have arisen in the ischemic section of the intestine. A more pronounced inflammatory reaction can now make the ischemic loop rigid and reduce its motor activity. This influences the propulsive motility in the proximal section of the intestine and the gastric emptying capacity.

Since, after 3 days, evacuation of the stomach again tended to become more effective and the distal propagation in the intestine to increase, such an inflammatory reaction in the ischemic section can be assumed to have mainly subsided. The indicated tendency to more effective propulsive functions can now again be elicited by local irritation of the neuromuscular system, which the remaining, moderate, intestinal ischemia can cause, and which results in eliciting propulsive acceleration.

This tendency was still active after 7 days, when both gastric emptying and intestinal propulsion were somewhat superior to the corresponding functions in the LC group. Analogously with previous discussions, it is assumed that at this stage a certain degree of ischemia still persisted; and that this continued to cause irritation which induced an acceleration of motility in the intestinal loop.

If the effect of laparotomy can be regarded as being entirely eliminated after 14 days, which is highly probable, then, however, the gastrointesti-

nal propulsive motility is normalized, which indicates that the damage caused by the local ischemia is now healed.

When a higher degree of local, intestinal ischemia had been induced by the ligation of 11 mes end arc, the initial effect on the gastric and intestinal propulsive functions was, on the whole, identical with the conditions in the LC group. Thus, gastric emptying was greatly retarded, and the part of the dose evacuated into the intestine was distributed strictly proximally. Acceleration of the propulsive functions, which was observed when the ischemia was less extensive (7 mes end arc) did not occur in this series. The cause of this may be, that the more pronounced ischemia damaged the neuromuscular structures of the loop to such an extent that it was no longer possible to elicit the hypothetical and accelerative long reflex.

Such a view can be supported by the conditions after 24 hours. Both the gastric emptying and the intestinal propagation of the dose showed a tendency to become inhibited; and this was evident to a greater extent than when the ischemia was less pronounced (7 mes end arc). It appears reasonable to suppose that tissue damage and consequent inflammatory reactions were more manifest. Locally, the propulsive effectivity was reduced, resulting in a stronger effect both on the proximal section of the intestine and on the stomach.

After 3 days this condition had changed. The gastric emptying and propulsion in the small intestine were now more effective, and corresponded to these functions in the case of milder ischemia (7 mes end arc). (After 2 hours, however, the gastric emptying was somewhat retarded in group 11 mes end arc, but the distal building up of the dose in the intestine was just as pronounced as in group 7 mes end arc.) Just as under milder ischemia the local tissue reaction seemed to have decreased. The cause of the rather more effective gastrointestinal propulsion may be the reappearance of such a local effect that stimulates the neuromuscular apparatus; possibly with the release of a long intestinogastric reflex, which gives rise to acceleration.

After 7 days the gastrointestinal propulsion was of the same character as that under more mild ischemia; and there was still a tendency towards more effective functions than in the laparotomized control group.

At the outset, there had been great reduction in propulsion when ischemia was more pronounced; this was especially noticeable after 24 hours. After 7 days, however, this reduction had greatly decreased and had, in part, been transformed into its opposite.

After 14 days the more pronounced intestinal ischemia showed a tendency to retard gastric emptying and to cause a more proximal distribution of the intestinal contents than after 7 days. Whereas the group subjected to moderate ischemia (7 mes end arc) had, after 14 days, a completely normalized gastric emptying and intestinal propulsion, the group subjected to pronounced intestinal ischemia (11 mes end arc) had a tendency to inhibit both functions. It has been known for a long time that an intestine, which has sustained circulatory damage, often heals with the formation of scars and strictures (Garré, 1892; Ginzburg & Klein, 1928; Ginzburg & Oppenheimer, 1933; Barry, 1942; Hurwitt *et al.*, 1953, and others). With such extensive ischemia as that obtained by the ligation of 11 mes end arc, there is reason to assume that the retarded propulsive functions after 14 days were due to fibrosis of the intestinal wall, whose neuromuscular structures were entirely or partly abolished and replaced by connective tissue. The segment of the intestine is converted into a comparatively stiff and, as regards motor capacity, ineffective tube, with or without relative stenosis. That this was actually the case, was verified by the histologic investigation (see Chapter VIII).

SUMMARY

The effect of laparotomy, on the gastrointestinal propulsive motility, with initially, greatly retarded gastric emptying and arrested distal distribution of the intestinal contents, had almost disappeared after 7 days.

When there was moderate intestinal ischemia (7 mes end arc) the emptying of the stomach was initially accelerated, and the distal distribution of the intestinal contents was more rapid. Such moderate intestinal ischemia was assumed to cause changes in the intestinal loop, which, through irritation of a presumed neuromuscular receptor mechanism, cause accelerated gastrointestinal propulsion. The somewhat reduced propulsion, which occurred after 24 hours, was

correlated with a more pronounced, local, inflammatory reaction in the ischemic section, with consecutively reduced propulsive effectiveness. The latter in turn affects the proximal section of the intestine and probably also the stomach.

When, after 3-7 days, the inflammatory reaction was regarded as having decreased, and a tendency to accelerated propulsive function reappeared, this was assumed to have been elicited by a now reduced, local, inflammatory-ischemic effect, which possibly stimulated the actual functions.

On the assumption that the effect of laparotomy had ceased after 14 days, the effect of moderate ischemia was considered to have ceased by that time.

Initially, when there was more extensive ischemia (11 mes end arc), both gastric emptying and intestinal propagation were arrested to the same substantial extent as after laparotomy, *i.e.* no isolated ischemic effect could be distinguished. Seen in relation to the more mild ischemia, it might possibly be assumed that the receptor mechanism, for the presumed long intestinal reflex, was absent, because of the higher degree of ischemia. After 1-7 days, gastrointestinal propulsion was similar in both the ischemic groups; but, after 14 days under the influence of pronounced intestinal ischemia (11 mes end arc), gastric emptying and the distal propagation of intestinal contents were retarded. Pronounced fibrosis, in the ischemic section, was now assumed to interfere, in this way, with normal gastric emptying and propulsion in the small intestine.

Chapter VII. Mathematical Analysis of the Quantitative Distribution of the Test Dose in the Small Intestine

ANALYTICAL PRINCIPLES

Grevsten, Johansson & Nylander (1967) have previously demonstrated a special ratio method for the analysis of the propulsive motility in the small intestine. According to this method, propagation of intestinal contents, is placed in relation to gastric emptying according to the formula:

$$\mu_i = \frac{x_i}{V + \sum_{j=1}^{i-1} x_j}$$

in which

μ_i = the ratio for fraction i (the term fraction is used with its previously defined meaning);

x_i = the part (in per cent) of the radioactive dose in fraction i ;

V = the part (in per cent) of the radioactive dose in the stomach;

$\sum_{j=1}^{i-1} x_j$ = the part (in per cent) of the radioactive dose in all the fractions proximal to the given fraction i .

Gastric emptying is assumed to have an exponential character under normal conditions. If the mathematical functions for propulsion in the small intestine and gastric emptying are identical, then μ_i is constant in all the fractions of the small intestine. If not, μ_i will vary, which will make it difficult to interpret the reciprocal relations of the motility functions. On the basis of the interaction between the functions in an intact normal material, the deviations caused by the experimental measures applied, can be assessed.

RESULTS AND CONCLUSIONS

In Tables XIII–XV μ_i values are given for all the experimental groups and experimental periods. The corresponding values are illustrated graphically in Figs. 18–29. Values for the distal fractions of the small intestine, containing less than 5% of the total dose are not given.

The μ_i values for the IC group for the experimental periods 30 and 60 minutes have been taken from an earlier study (Nylander & Wikström, 1968), as well as the values for the groups LC-0 day, 7 mes end arc-0 day, and 11 mes end arc-0 day for the experimental period of 60 minutes.

Group IC had, for the experimental periods 30 and 60 minutes, μ_i values which were maximal in fractions 5–6. This peak was interpreted as an expression of decreased propulsive activity, or passivity, in the intestine distal to this level. Another group of intact control animals that were analyzed by Grevsten, Johansson & Nylander (1967), showed results which, in principle, were entirely in agreement with these.

In the following the assumption will be made that gastric emptying and propulsive motility of the small intestine have the same exponential course as under normal conditions. On the basis of the results for the IC-group, it is assumed that μ_i approximates 0.13.

Group LC is shown in Table XIII and Figs. 18 and 19.

In group LC-0 day (analysis in immediate connection with laparotomy), the μ_i value after one hour was 0.18 for fraction 1 and for fraction 2 = 0.10. Thus, there was some accumulation of the evacuated part of the dose already in fraction 1. Distal to this it was assumed that the intestine was propulsively passive. The distal front of the dose was represented by fraction 3, whereas in the IC-group, after the corresponding period, it had extended to fraction 9. The stomach was essentially passive or had begun to empty very slowly.

After 24 hours the evacuative function of the stomach had improved substantially (see also Chapter VI). This applied also to the intestinal function. At the experimental period of 30 minutes (Fig. 18) the μ_i values of the fractions were comparatively constant. This could be taken as

TABLE XIII. Quotient values (μ_i) in the LC group in different experimental conditions

Small intestinal fraction	Experimental period in min.							
	30			60			120	
	Pre-exp. interval in days							
	1	3	7	1	3	7	1	3
1	0.06	0.11	0.11	0.07	0.08	0.12	0.18	0.12
2	0.07	0.12	0.15	0.09	0.10	0.14	0.15	0.17
3	0.08	0.15	0.22	0.13	0.16	0.16	0.17	0.19
4	0.08	0.17	0.24	0.15	0.12	0.32	0.37	0.28
5	0.10	0.16	0.19	0.13	0.18	0.37	0.35	0.34
6	0.09	0.12	0.12	0.13	0.18	0.27	0.26	0.37
7	0.07	0.09	0.07	0.13	0.14	0.12	0.19	0.20
8	0.05	0.07		0.09	0.07		0.19	0.11
9							0.11	0.16
10								0.08
<i>n</i>	15	15	21	15	15	21	20	20

indicating that the functions representing gastric emptying and propulsion in the small intestine were approximately identical. After both 30 and 60 minutes the distal front of the dose had extended to fraction 8. At the longer experimental period the μ_i level was higher. Thus, the recoveries of the propagative functions of the stomach and the small intestine were in reciprocal agreement.

After 3 days both the gastric evacuative function and the propulsive activity of the intestine showed further improvement (see Chapter VI and Figs. 18-19). The distal front of the dose was still represented, however, by fraction 8. At the experimental time of 60 minutes there was an indication that the μ_i values reached a peak in fractions 5-6. Despite substantially lower μ_i val-

ues, this peak corresponded essentially with the situation in the intact control animals.

The relation between the propulsive effect of the stomach and that of the small intestine had thus been normalized, with a comparatively passive small intestine distal to this level.

When 7 days had passed both the emptying of the stomach and the intestinal propulsion were similar to the conditions in the IC group (see Chapter VI). A distinct peak in the μ_i values was identified in fraction 5. The corresponding peak in the IC group was situated in fraction 6. The more proximal location of the peak corresponded to the location of the propagation front in the LC group in fraction 7, whereas in the IC group it extended to fraction 9. These conditions may indicate that the propulsive functions were norma-

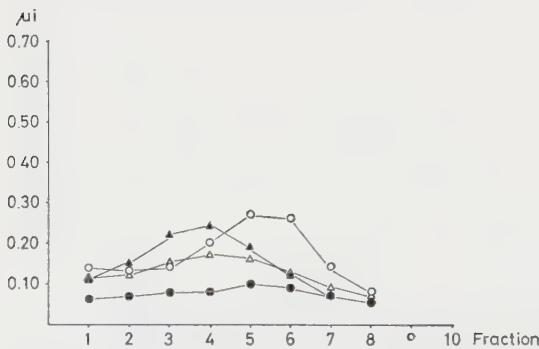


Fig. 18. Graphic representation of ratio values (μ_i) for the consecutive, equal-sized fractions of the small intestine. Experimental period 30 min. $\circ$, IC; $\bullet$, LC 1 day; $\triangle$, LC 3 days; $\blacktriangle$, LC 7 days.

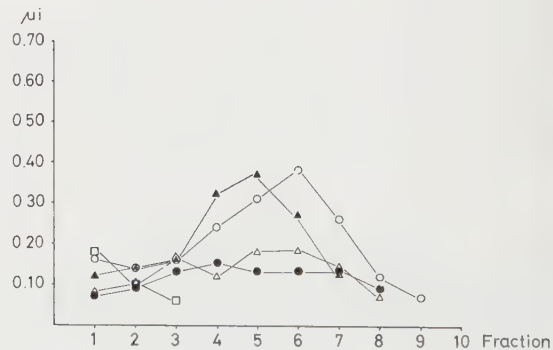


Fig. 19. Graphic representation of ratio values (μ_i). Experimental period 60 min. $\circ$, IC; $\square$, LC 0 day; $\bullet$, LC 1 day; $\triangle$, LC 3 days; $\blacktriangle$, LC 7 days.

TABLE XIV. Quotient values (μ_i) in the 7 mes end arc group in different experimental conditions

Small intestinal fraction	Experimental period in min.											
	30				60				120			
	Pre-exp. interval in days											
	7	14	1	3	7	14	1	3				
1	0.09	0.10	0.08	0.07	0.11	0.07	0.11	0.07				
2	0.11	0.15	0.14	0.10	0.10	0.13	0.10	0.06				
3	0.21	0.15	0.18	0.12	0.14	0.17	0.09	0.18				
4	0.26	0.22	0.19	0.19	0.12	0.29	0.14	0.20				
5	0.24	0.29	0.16	0.34	0.29	0.56	0.20	0.25				
6	0.16	0.17	0.11	0.24	0.56	0.48	0.18	0.33				
7	0.12	0.11	0.07	0.18	0.39	0.29	0.21	0.35				
8		0.07		0.08	0.18	0.16	0.23	0.28				
9					0.08	0.05	0.14	0.32				
10								0.10				
<i>n</i>	24	29	20	22	26	25	21	24				

lized with regard to their reciprocal relations, but 7 days after laparotomy these functions in themselves were still not quite normal. These conditions are most apparent after an experimental period of 60 minutes (Fig. 19).

Group 7 mes end arc is shown in Table XIV, for all the subgroups and all the experimental periods, and in Fig. 20 for the common experimental period of 60 minutes.

Fig. 20 shows that immediately after the induction of ischemia, the μ_i level was about 0.20 in fractions 1-2 and subsequently, decreased. The distal front of the dose reached fraction 5. This very proximal accumulation in the small intestine was previously regarded as an indication that there was no similarly effective propulsion, in this

part of the small intestine, that corresponded to the initial acceleration of gastric emptying (Nylander & Wikström, 1968).

After 24 hours the μ_i values formed a slight peak in fraction 4; and the distal front of the dose was now represented by fraction 7. The intestine was considered, at this stage, to have regained in part its propulsive capacity—a condition which became more pronounced the longer the interval after the induction of ischemia (3, 7 and 14 days). The peak was thus shifted distally, so that after 3 days it corresponded to fraction 5, when the distal front of the dose reached fraction 8. After 7 and 14 days respectively, the peak values were higher and lay in the 6th and 5th fraction, but with further distal propagation of the front to fraction 9.

In group IC, the μ_i values formed a peak in fraction 6, and the distal front of the dose was represented by fraction 9. The fact that after 3-14 days the μ_i levels in group 7 mes end arc showed peaks situated increasingly more distal (fractions 5 and 6), and that the distal front of the dose extended successively further down, indicates that, with the lapse of time, the intestinal function regained a propulsive capacity which nearly corresponded with that of the group IC. The substantially higher μ_i values, which were represented by the peaks after 7 and 14 days, compared with conditions in the group IC, indicate that a local and moderate ischemic procedure causes an increase in the normally existing dif-

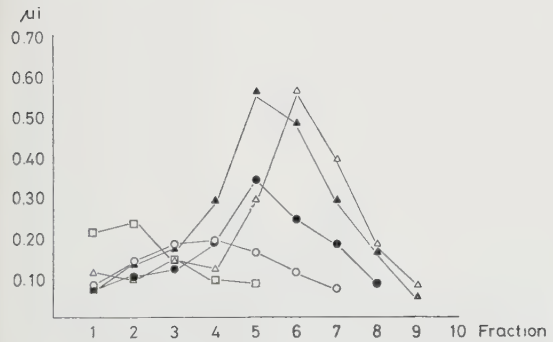


Fig. 20. Graphic representation of ratio values (μ_i). Experimental period 60 min. $\square$, 7 mes end arc 0 day; $\circ$, 7 mes end arc 1 day; $\bullet$, 7 mes end arc 3 days; $\triangle$, 7 mes end arc 7 days; $\blacktriangle$, 7 mes end arc 14 days.

TABLE XV. Quotient values (μ_i) in the 11 mes end arc group in different experimental conditions

Small intestinal fraction	Experimental period in min.											
	30				60				120			
	Pre-exp. interval in days											
	7	14	1	3	7	14	1	3				
1	0.09	0.12	0.12	0.07	0.07	0.07	0.10	0.09				
2	0.11	0.14	0.20	0.10	0.07	0.06	0.11	0.08				
3	0.18	0.25	0.22	0.16	0.19	0.09	0.12	0.08				
4	0.21	0.28	0.12	0.19	0.21	0.11	0.14	0.07				
5	0.19	0.35	0.11	0.25	0.43	0.28	0.16	0.17				
6	0.19	0.22	0.08	0.27	0.48	0.41	0.14	0.23				
7	0.14	0.10		0.20	0.37	0.22	0.11	0.33				
8	0.05			0.11	0.24	0.09		0.30				
9				0.05	0.14			0.23				
10								0.11				
<i>n</i>	23	27	20	22	25	28	20	22				

ference in propulsive effectiveness between the proximal and distal small intestine.

Group 11 mes end arc is presented in Table XV, with all the subgroups and all the experimental periods, and in Fig. 21 with the common experimental period of 60 minutes.

In the earlier part of this investigation (Nylander & Wikström, 1968) the poor emptying of the stomach was regarded as essentially corresponding to the likewise diminutive propagative function of the intestine in group 11 mes end arc-0 day at the experimental period of 60 minutes. As was previously mentioned, both gastric emptying and the propagation of the dose in the small intestine were greatly reduced, but apparently to the same extent. The distal front of the dose was

situated in fraction 3, and the μ_i values for fractions 1 and 2 were approximately 0.13.

Fig. 21 shows that in group 11 mes end arc, the intestine had, after 24 hours, recovered part of its propulsive capacity, so that the μ_i level formed a peak in fraction 3, and the front extended to fraction 6.

The same tendency to normalization of the propulsive capacity of the intestine, as that observed in the group subjected to more moderate ischemia (7 mes end arc), was present after 3–14 days. Thus, the μ_i level formed a peak in fraction 6, as was the case in group IC. The same tendency was observed, as that in group 7 mes end arc, namely, that the peaks after 7 and 14 days had higher μ_i values than those in group IC. The conclusion should be the same as that suggested for the group 7 mes end arc, namely, that the normal breaking level, between effective and less effective intestinal propulsion, is more pronounced. The differences in the results obtained after 7 and 14 days are apparently paradoxical. After 14 days the μ_i level was lower throughout and the front of the dose was located less distally than after 7 days. As previously pointed out, both gastric emptying and distal distribution of the dose in the small intestine were then less effective—an inhibition which, judging by the symmetry of the diagram, affected the stomach and the intestine to the same extent.

Figs. 22–29 show the μ_i values for the ischemic groups (7 and 11 mes end arc) for the same pre-experimental time.

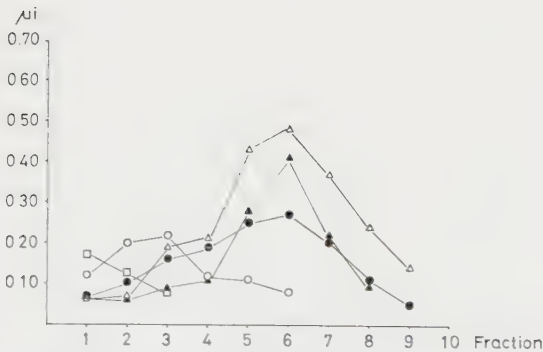


Fig. 21. Graphic representation of ratio values (μ_i). Experimental period 60 min. $\square$, 11 mes end arc 0 day; $\circ$, 11 mes end arc 1 day; $\bullet$, 11 mes end arc 3 days; $\triangle$, 11 mes end arc 7 days; $\blacktriangle$, 11 mes end arc 14 days.

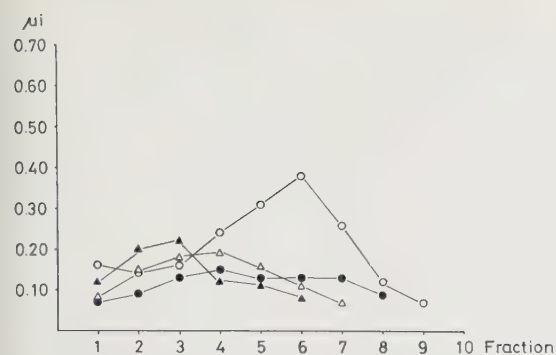


Fig. 22. Graphic representation of ratio values (μ_i); 1 day after surgery. Experimental period 60 min. $\circ$, IC; $\bullet$, LC; $\triangle$, 7 mes end arc; $\blacktriangle$, 11 mes end arc.

Fig. 22 shows that after 1 day and at the experimental period of 60 minutes the propulsive capacity of the intestine was, as far as it could be assessed by this method, most reduced in the group 11 mes end arc, where the μ_i peak occurred already in the 3rd fraction, and where the front extended only to fraction 6. When the experimental period was prolonged to 120 minutes the retardation of the front was most pronounced (Fig. 23). The LC group had now a higher μ_i level than the ischemic groups, and a definite peak in the 4th fraction. Thereafter, the μ_i level was high throughout, up to and including fraction 8. In the group 7 mes end arc there was a peak in fraction 8 and a μ_i value which corresponded to that in the LC group. In the groups LC and 7 mes end arc the front extended to fraction 9. These conditions indicate that after 24 hours the propulsion in the small intestine had made a better recovery in the groups LC and 7

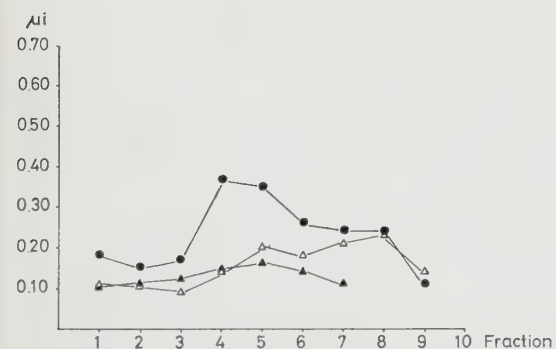


Fig. 23. Graphic representation of ratio values (μ_i); 1 day after surgery. Experimental period 120 min. $\bullet$, LC; $\triangle$, 7 mes end arc; $\blacktriangle$, 11 mes end arc.

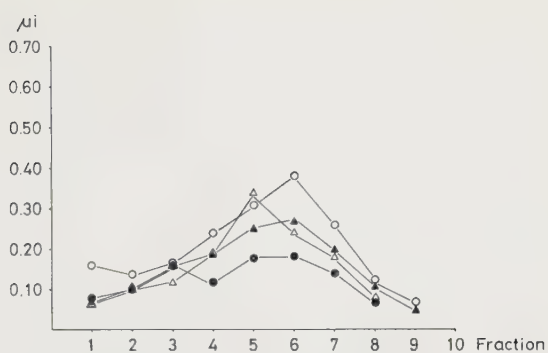


Fig. 24. Graphic representation of ratio values (μ_i); 3 days after surgery. Experimental period 60 min. $\circ$, IC; $\bullet$, LC; $\triangle$, 7 mes end arc; $\blacktriangle$, 11 mes end arc.

mes end arc than in the group subjected to the most extensive ischemia (11 mes end arc).

After 3 days the ischemic groups showed, according to this method, a greater tendency than the LC group to normalize the propulsive function of the intestine. At the experimental period of 60 minutes (Fig. 24), the ischemic groups showed higher μ_i values (to whose significance, however, too much importance should not be attached) than group LC, with peaks in fractions 5 and 6. The μ_i values in the IC group formed a peak in fraction 6. There was a tendency also in the ischemic groups for the dose to be more distally distributed than in the LC group. When the experimental period was extended to 120 minutes (Fig. 25), this tendency still persisted. These conditions were considered to indicate that after 3 days the propulsive function of the intestine was more effective in the ischemic groups than in group LC.

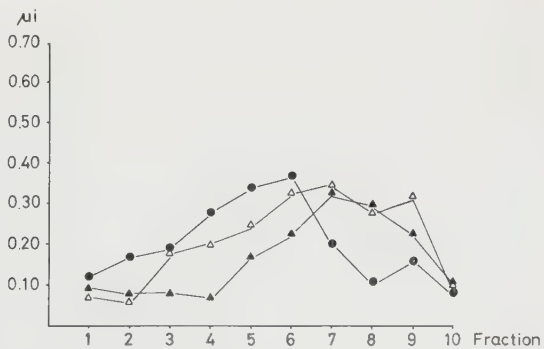


Fig. 25. Graphic representation of ratio values (μ_i); 3 days after surgery. Experimental period 120 min. $\bullet$, LC; $\triangle$, 7 mes end arc; $\blacktriangle$, 11 mes end arc.

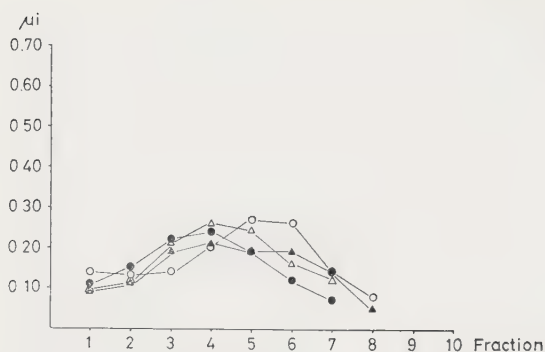


Fig. 26. Graphic representation of ratio values (μ_i); 7 days after surgery. Experimental period 30 min. ○, IC; ●, LC; △, 7 mes end arc; ▲, 11 mes end arc.

Figs. 26 and 27 show the μ_i values for the different experimental groups after 7 days. At the experimental period of 30 minutes (Fig. 26) there was no distinct difference between the groups. In both the group LC and the ischemic groups the μ_i values formed a peak in fractions 4-6. At the longer experimental period of 60 minutes (Fig. 27), in the ischemic groups there was a higher peak of the μ_i level than in the IC and LC groups. Peak formation in the ischemic groups occurred, however, in the same fraction (6) as that in the IC group. The distal front extended to fraction 9 in both the ischemic groups and the IC group. In group LC the μ_i showed a peak in fraction 5; and the front extended only to fraction 7. Thus, after 7 days the propulsive function was more effective in the ischemic groups than in group LC. The μ_i peaks of the ischemic groups were situated in the same fraction as in group IC;

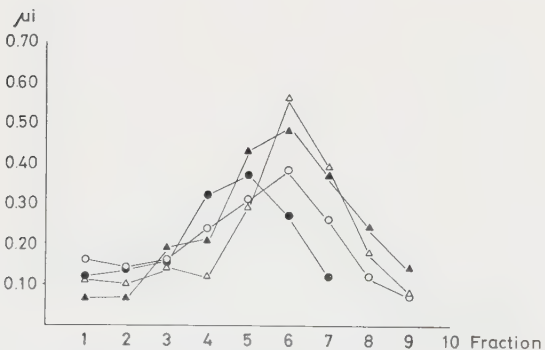


Fig. 27. Graphic representation of ratio values (μ_i); 7 days after surgery. Experimental period 60 min. ○, IC; ●, LC; △, 7 mes end arc; ▲, 11 mes end arc.

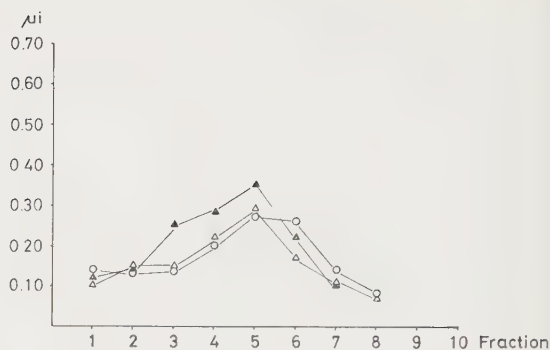


Fig. 28. Graphic representation of ratio values (μ_i); 14 days after surgery. Experimental period 30 min. ○, IC; △, 7 mes end arc; ▲, 11 mes end arc.

and the distal front of the dose had advanced the same distance. These conditions may indicate a normalization of the intestinal function, in the ischemic groups, after 7 days. The significance of the higher μ_i peaks (compared with group IC) has been discussed previously.

Figs. 28 and 29 demonstrate the μ_i values of the ischemic groups after 14 days. At the experimental period of 30 minutes (Fig. 28) there was no basic difference between the ischemic groups and group IC. In all the groups the μ_i peak was in fraction 5, and the distal front was at the same level. At the longer experimental period of 60 minutes (Fig. 29) there was the same tendency for the μ_i values to become normalized in the ischemic groups although the μ_i peak in the 7 mes end arc group was on a higher level and very slightly proximal to the peaks in the 11 mes end arc group and group IC.

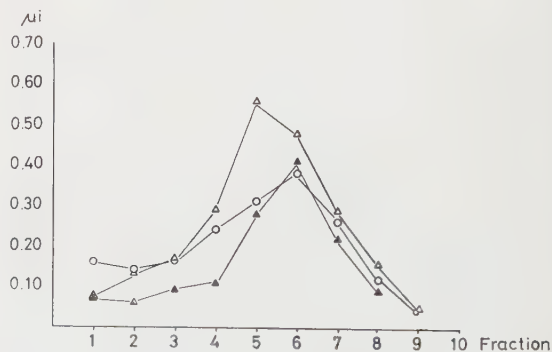


Fig. 29. Graphic representation of ratio values (μ_i); 14 days after surgery. Experimental period 60 min. ○, IC; △, 7 mes end arc; ▲, 11 mes end arc.

DISCUSSION

Grevsten, Johansson & Nylander (1967) have previously demonstrated that gastric emptying and propagation of contents in the small intestine, under normal conditions, are identical functions from a mathematical point of view. This held good for the initial phase of the intestinal distribution of a test substance. During a later phase this condition applied only to the proximal 3/5 of the small intestine. In the remaining part propulsive activity was obtained only later, when the contents passed into the colon (Johansson & Nylander, 1968).

With this analytical technique Nylander & Wikström (1968) investigated the immediate effect of laparotomy and local ischemia of the small intestine, on the quantitative distribution of a test substance in the small intestine.

The immediate effect of laparotomy was that the intestine became propulsively passive distal to the first fraction. With lapse of time after the intervention, the intestinal propulsion improved successively and, after 7 days, the μ_i values had assumed a pattern which closely corresponded to that of group IC. In the group LC, however, both the μ_i peak and the distal front of the dose were more proximally orientated and, consequently, it was considered that the effect of the laparotomy *had not entirely disappeared after 7 days*.

With moderate, local, intestinal ischemia (7 mes end arc) the propulsive function of the intestine was, initially, better than in group LC, but after fraction 2 the intestine was, essentially, propulsively passive. With lapse of time, the propulsive function of the intestine improved and after 3 days the μ_i values had assumed a pattern that closely corresponded with that of group IC. After 7 days, in the ischemic group, the μ_i peak was formed in the same fraction as in the group IC; and the distal front was similar; consequently, the propulsive capacity of the intestine was judged to be normalized. After 14 days, in principle, the same conditions prevailed, but the μ_i peak was, after both 7 and 14 days, significantly higher than in the group IC. The breaking level between propulsively active and less active small intestine was more pronounced in these groups. This probably indicates that the small intestine, distal to this level, is more definitively passive (paretic ?).

When subjected to a higher degree of ischemia (11 mes end arc) the small intestine was, initially,

propulsively passive to the same extent as the group LC. With lapse of time after induction of the ischemia, the intestine regained its propulsive capacity. As in the group that had been subjected to moderate ischemia, after 3 days the μ_i pattern corresponded closely with that of the group IC. After 7 days the propulsive function when calculated in this way, was normalized, with the μ_i peak in the same fraction as that in the group IC, and also with the distal front at the same level. As in the foregoing group, the μ_i peak in the ischemic group was considerably higher than in the group IC. A more pronounced loss of motility distally may be assumed to be the cause. After 14 days the μ_i level was lower throughout and the dose less distally advanced than after 7 days. This condition is worthy of note and indicates that *the propulsive intestinal function had deteriorated*. In the light of the considerations discussed in chapter VI, fibrosis had probably developed in the ischemic section, causing, in the first place, disturbances in intestinal propulsion, but also in gastric emptying.

The mathematical analysis confirmed essentially the results and conclusions reported earlier with regard to the gastrointestinal propulsive motility (Chapter VI).

Chapter VIII. Microscopic Observations

The surgical ischemia caused characteristic changes in the intestinal section studied. On the basis of the macroscopic appearance of the ischemic segment, the material was divided into 3 different types. These were defined in Chapter VI. It appeared desirable, however, to study more closely the character of the changes by histologi-

cal analysis of the small intestine in and around the ischemic zone.

MATERIAL AND METHODS

The small intestine was investigated in 40 animals subjected to regional intestinal ischemia as re-

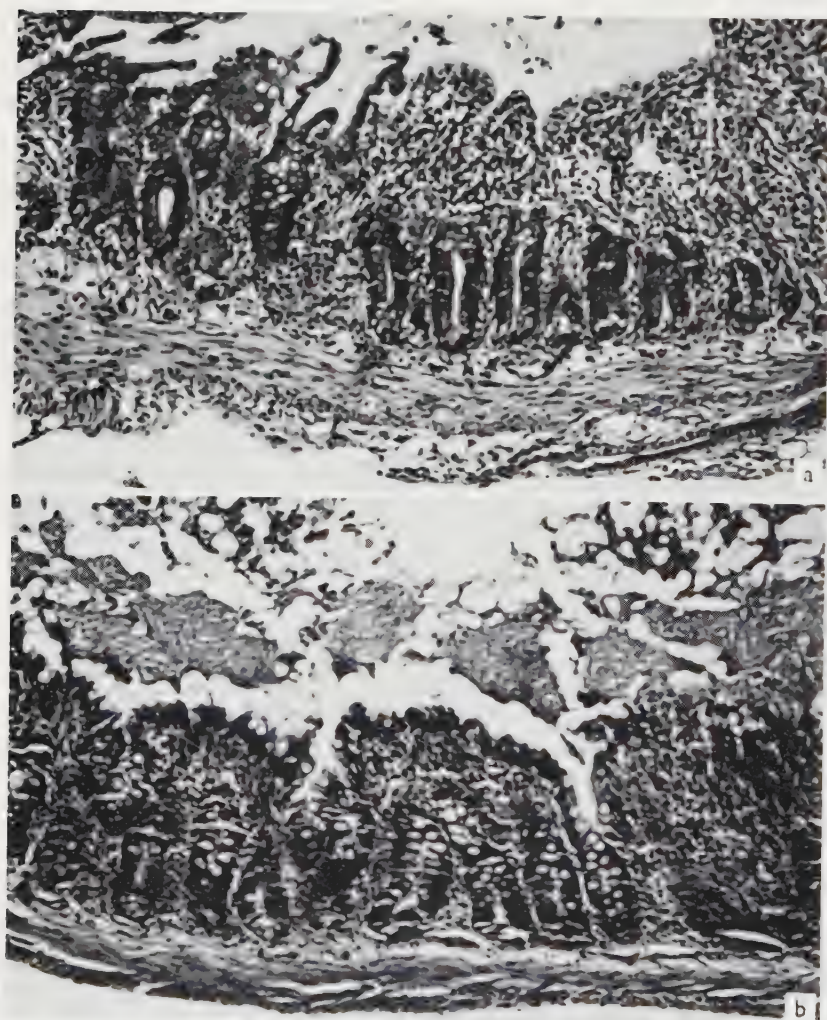


Fig. 30. Sections from the central part of the small intestinal loop subjected to surgical ischemia (7 mes and arc) 1–14 days after its induction (a–d). (a) Duration of ischemia: 1 day. The inflammatory cell infiltration is pronounced especially in the villi. (b) Duration of ischemia: 3 days. Epithelial

degeneration and desquamation dominate the picture. (c) Duration of ischemia: 7 days. Regeneration of villi. (d) Duration of ischemia: 14 days. Regeneration of villi now complete. Goblet cells dominate. Fibrosis in the deeper layers ($\times 100$).

ported in Chapter VI. The material was divided as follows:

The small intestine with the macroscopic character of type I (see p. 17) was analyzed in the groups 7 and 11 mes end arc on all the previously stated occasions (1-14 days).

Changes of types II and III were investigated only in group 11 mes end arc, 14 days after the induction of ischemia.

In each case, material for microscopic investi-

gation was taken from 4 different, well-defined levels of the small intestine as indicated below:

1. Immediately distal to the duodenum.
2. Directly proximal to the ischemic section.
3. Centrally in the ischemic section.
4. Directly distal to the ischemic section.

In immediate connection with the termination of the gastrointestinal motility studies (at most 30 minutes after the animal was killed), tissue spe-

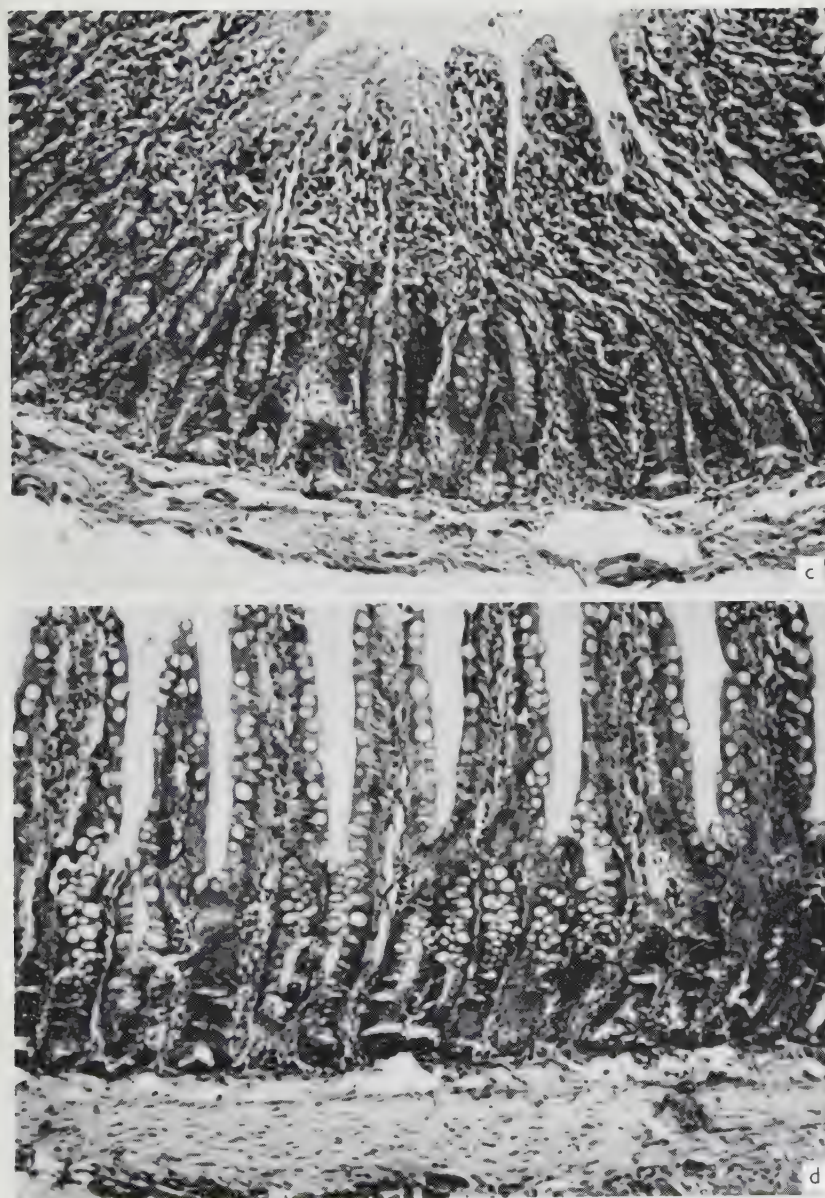


Fig. 30 c, d.



Fig. 31. Sections from the central part of the small intestinal loop subjected to surgical ischemia (11 mes end arc) 1–14 days after its induction (a–d). (a) Duration of ischemia: 1 day. Oedema and inflammatory cell infiltration throughout the intestinal wall. (b) Duration of ischemia: 3 days. The desquamation of the mucosa is almost complete. Inflammatory cell

infiltration pronounced. (c) Duration of ischemia: 7 days. Regeneration of the mucosa is in progress from the crypts. Note the dense fibrosis in the deeper layers. (d) Duration of ischemia: 14 days. Regeneration of the mucosal layer is completed. Goblet cells dominate. Fibrosis in the deeper layers ($\times 100$).

cimens were excised from these sections of the intestine. Preparations of suitable size were fixed in 10% neutral formalin, or in Zenker's fixative. Staining was carried out with hematoxylin eosin.

RESULTS

In type I the intestine showed an essentially normal micromorphology at levels 1, 2 and 4 as enumerated above.

In Figs. 30 and 31 histologic sections are presented from the ischemic loop (intestinal level 3 according to the above scheme). When ischemia (7 mes end arc) had continued for 1 day (Fig. 30 a), oedema and inflammatory cell infiltration were comparatively prominent features. The epithelium was relatively intact and without desquamation. After 3 days (Fig. 30 b) the oedema and inflammatory cell infiltration had decreased, but

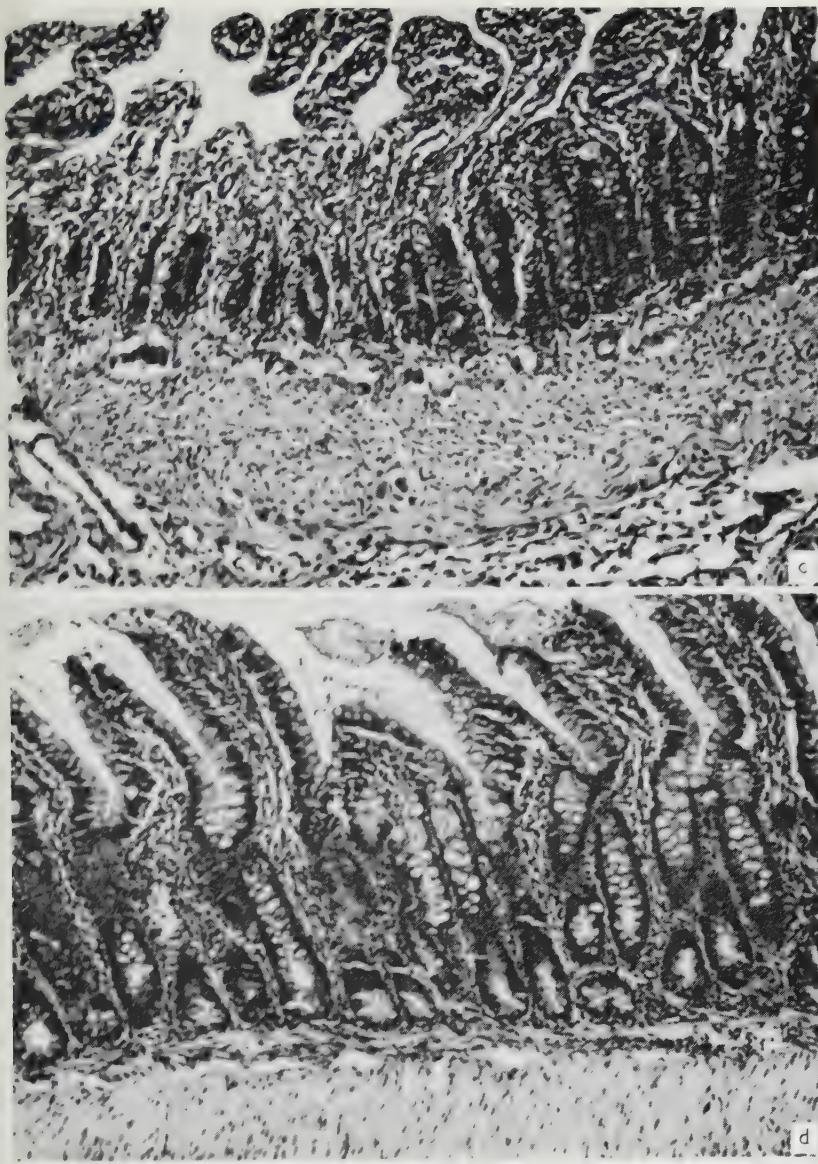


Fig. 31 c d.

now the epithelium covering the villi and in places the whole structure exhibited definite degeneration and desquamation. The intestinal lumen contained an abundance of such debris. After 7 days (Fig. 30 c) regeneration of the epithelium and the mucous membrane had begun to some extent. The deeper layers of the intestinal wall seemed to be intact.

After 14 days (Fig. 30 d) the villi had regenerated and were well formed. Goblet cells were

dominant in the epithelium. In the submucosa and the muscle layers there was (slight) fibrosis.

When there was more pronounced intestinal ischemia (11 mes end arc), after 1 day (Fig. 31 a) there was, possibly, more pronounced oedema and more abundant infiltration of inflammatory cells in both the villi and the rest of the intestinal wall, whose epithelium, however, had not yet desquamated.

After 3 days (Fig. 31 b) on the other hand, the

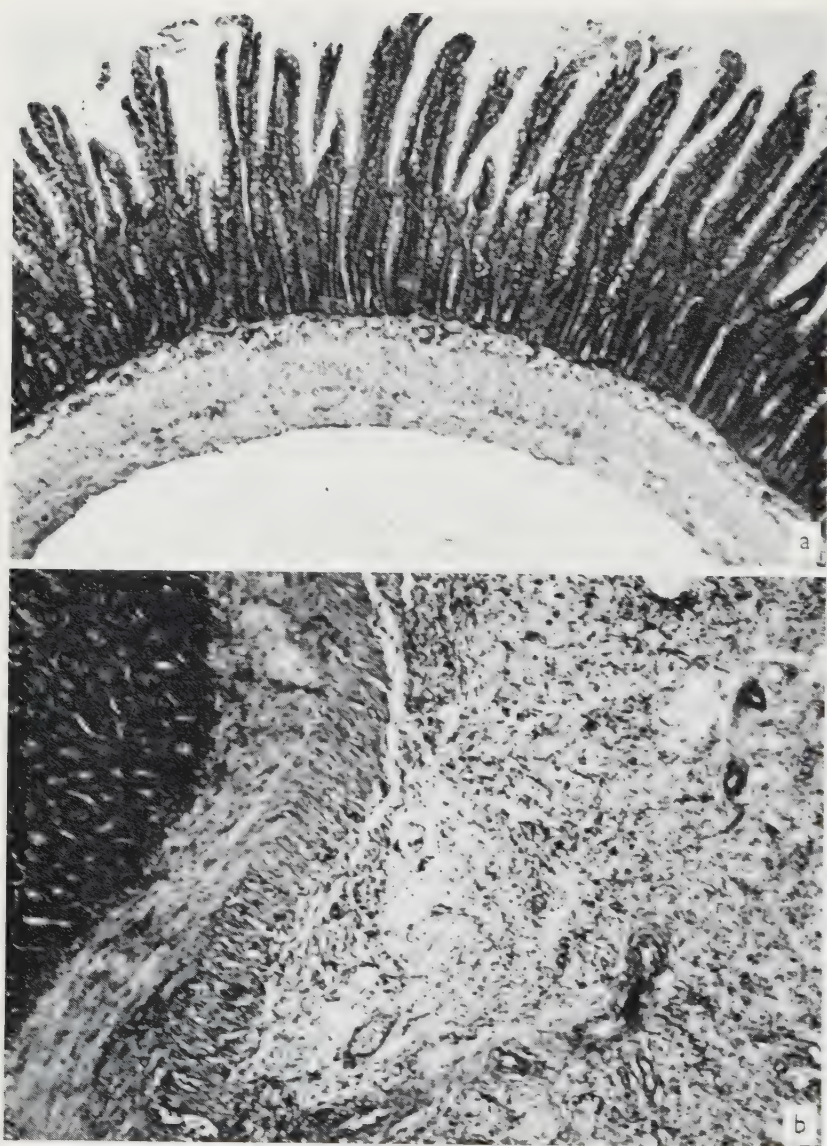


Fig. 32. Sections representing the small intestine at a level above (a) and in (b) the ischemic section. In the former case (a) the intestinal wall is moderately thickened by fibrosis and smooth muscle hypertrophy. In the ischemic section proper (b) the fibrosis is abundant but the epithelial layer still intact (x 40).

epithelium covering the villi, and in some places the whole mucous membrane, were denuded, and varying stages of extensive desquamation dominated the picture. But here, as in all the other sections the basal glandular crypts were still intact.

After 7 days (Fig. 31 c), extensive regeneration of the epithelium had set in. In the deeper mural layers fibrosis had become manifest.

After 14 days (Fig. 31 d), Goblet cells were predominant in the epithelium and the histologic picture in the deeper mural layers was dominated by pronounced fibrosis, which substantially thickened the intestinal wall.

Types II and III have been included in the present report in order to elucidate the pathohistology when the local, ischemic effect was more pronounced. Types II and III are presented in Fig. 32 and 33, where, in addition to intestinal level 3, intestinal level 2 has also been included.

In Type II fibrosis of the wall and smooth muscle hypertrophy was suggested already proximal to the ischemic section (Fig. 32 a).

In the latter (Fig. 32 b) the intestinal wall was the site of massive connective-tissue proliferation, but the lumen was still covered with epithelium.

In Type III (Fig. 33 a) the intestinal wall, im-

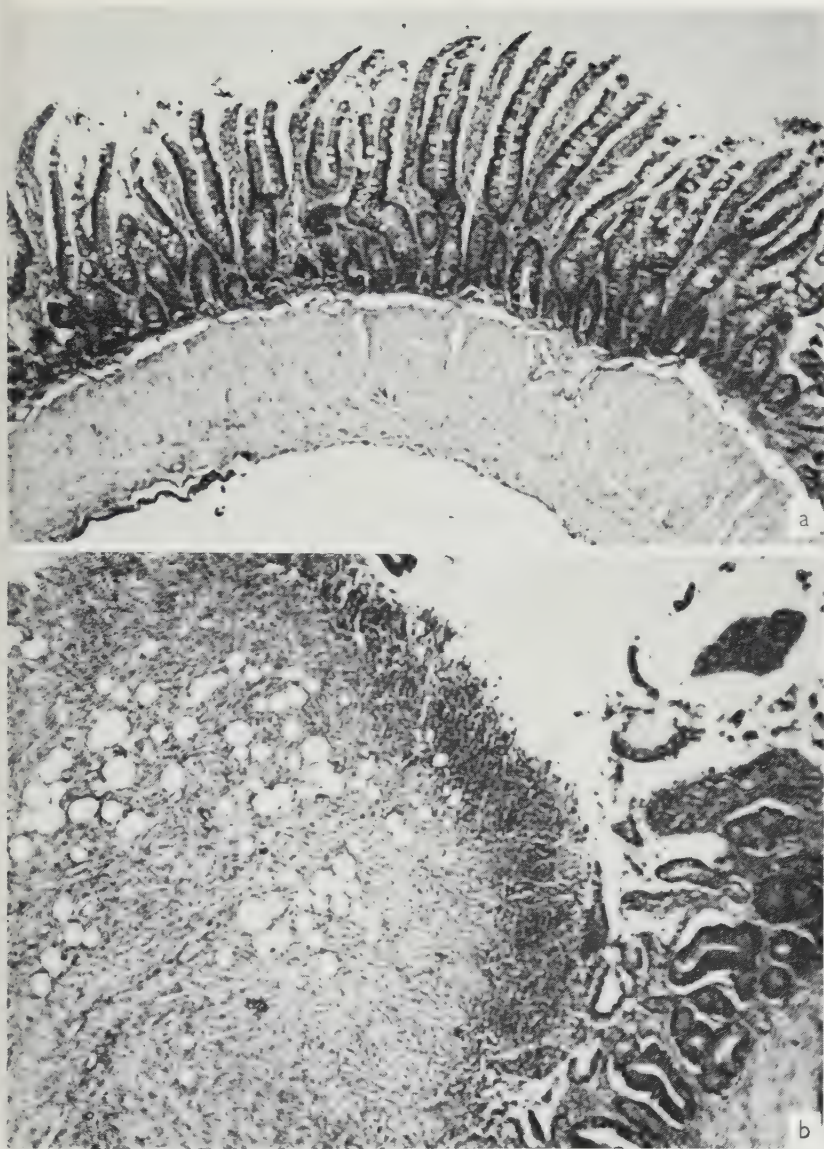


Fig. 33. Sections representing the small intestine at a level above (a) and in (b) the ischemic section. In the former case (a) the intestinal wall is appreciably thickened by fibrosis and smooth muscle hypertrophy. In the ischemic section proper (b) the abundant scar tissue is devoid of any epithelium ($\times 40$).

mediately proximal to the ischemic section, was dominated by smooth muscle hypertrophy and connective tissue to a greater extent than in Type II. In the ischemic section the fibrotic transformation of the intestinal wall was almost total; and the covering epithelium had disappeared (Fig. 33 b). Strictures, due to contracted scars, were manifest.

SUMMARY AND DISCUSSION

When intestinal ischemia was more moderate (7 mes end arc) as well as when it was more pronounced (11 mes end arc), after 1 day, there was,

in the ischemic segment, an inflammatory reaction in the intestinal wall, with oedema and inflammatory cell infiltration. After 3 days the dominant feature was that the epithelium covering the villi, and to some extent even the whole structure, were desquamated to varying degrees. When 7 days had elapsed, new epithelium had been formed; and when intestinal ischemia had been pronounced, the inflammatory reaction was followed by more or less pronounced fibrosis. After 14 days especially the group that was subjected to more pronounced intestinal ischemia, had developed marked fibrosis in the intestinal wall. In

Types II and III the increased fibrosis appeared as a more pronounced local effect of the surgical ischemia. This fibrosis had then a very *proliferative* character, and led to the formation of strictures. *The histologic observations reported here verified essentially the previously indicated occurrence of both an early inflammatory phase, and a subsequently developed, mural fibrosis in the ischemic section of the intestine.*

Chapter IX. General Discussion

An intestine that has sustained circulatory damage and survives, does not, in many cases, regain its normal peristalsis. On one hand, the neuromuscular function of the intestine may be disturbed. Raw (1943) alluded to such cases as "physiologic stricture". In more serious conditions of ischemia, scar formation in the wall, with secondary strictures is a usual late complication (Garré, 1892; Barry, 1942; Raw, 1943; Grisell, 1949; Wangenstein, 1942).

In this work I have studied the effect which ischemia (defined with regard to its location and extent) in the small bowel exerts on gastrointestinal propulsion during a period of 14 days following its surgical induction.

In order to obtain a quantitatively standardized ischemia in a definite loop of the small bowel, its mesenteric vessels were ligated peripherally. The ligatures were placed at the vascular bifurcations close to the mesenteric attachments. In the rat these form connections between adjacent secondary vascular arches. The vascular bifurcation is called here a mesenteric end arcade. On the ligation of a consecutive number of such arches the anastomotic flow was of necessity weakest centrally in the devascularized part of the intestine. Consequently, the maximal effect of the ischemic procedure was evaluated there.

In view of the fact that devascularization was always begun at a constant distance from the ileo-caecal angle, essentially the same part of the intestine was subjected to ischemia in all the cases. In order to obtain a quantitative evaluation of the ischemia, a segment was chosen which was of constant size and situated centrally in the devascularized section. The passive absorption of a radioactive test substance from this segment, was taken as an expression of the exchange circulation in its mucosa. Since the animals were identical from the point of view of iodine metabolism, and the iodide concentration of the test solution was constant and, moreover, the size of the mucosal area was always the same, the exchange circulation in the mucosa was the only variable in the experimental groups. The method was used

successfully by Nylander & Wikström (1968) and proved to be a good quantitative indicator of local ischemia. Only when 7 consecutive mes end arc had been ligated was ischemia so pronounced that passive absorption of iodide was significantly retarded. The greater the number of mesenteric vessels ligated the more this absorption was decreased.

In this investigation only a moderate ischemia (7 mes end arc) has been evaluated according to this principle, and that not until 7 and 14 days after its induction. For such a moderate degree of ischemia and after so long a time, the possibility of radio-iodide diffusing through the wall of the isolated intestinal loop into the peritoneum was regarded as excluded. Even when there was such pronounced ischemia as resulted from the ligation of 15 mes end arc and in close connection with its induction, merely 5% of the dose leaked through the intestinal wall. When ischemia was considerably less, such leakage was considered improbable.

With such ischemia passive absorption of iodide from the loop had further deteriorated after 7 and 14 days respectively. Thus, the exchange circulation of the intestinal mucosa might have decreased, and consequently the ischemia increased. Secondary effects of ischemia such as form part of the process of healing and cause fibrosis, may be assumed to be implicated, an assumption that has been verified by means of histologic analysis.

In a series of *in vitro* experiments the corresponding intestinal loop showed *increased* permeability to iodide after ischemia of this kind. That this condition was the result of an ischemic damage was all the more evident, when laparotomy alone *reduced* the permeability (Nylander & Wikström, 1968). The diminished permeability produced by laparotomy was more pronounced after 24 hours; and was regarded as due to such exudation as is involved in the inflammatory reaction.

In my series of corresponding *in vitro* experiments, the group subjected to the lowest degree

of ischemia had now, 7 days after induction of ischemia, a transmural iodide leakage similar to that which occurred 7 days after laparotomy. This was also the normal permeability to iodide, since, under the same conditions, a similar amount penetrated the intestinal wall of intact animals. The inflammatory reaction, which caused reduced permeability and was a primary consequence of laparotomy, had decreased, as had also the immediate ischemic effect with its enhanced iodide permeation.

Fourteen days after the induction of ischemia the iodide leakage from the loop was substantially reduced. Such changes had now developed in the intestinal wall, owing to the ischemia, that permeation of iodide was inhibited. These findings were consistent with the pronounced changes with fibrosis in the intestinal wall, which the histologic investigation revealed.

The degrees of surgical ischemia applied had an effect on the propulsive motility of the gastrointestinal tract up to 14 days after its induction. The method employed for the quantitative evaluation of the gastrointestinal propulsion *in the closed abdomen* has been successfully applied earlier; and, like the mathematical method used for analyzing the results, has been discussed in detail (Derblom, Johansson & Nylander, 1963, 1966; Grevsten, Johansson & Nylander, 1967; Nylander & Wikström, 1968). The method records what is known as the *propulsive net effect*, i.e. the sum of such motor activity in the intestinal wall as contributes to the distal propagation of the intestinal contents. Gastric emptying and propulsion in the small intestine can be recorded simultaneously, and the differentiated propulsive motility in various parts of the small bowel can be related to the function of gastric emptying.

By obtaining in this way a quantitative expression for the propulsive motility of the gastrointestinal tract, it has been possible to determine the effect of the regional intestinal ischemia on the relevant functions.

Thus, the influence of both moderate and more pronounced regional intestinal ischemia has been analyzed up to 14 days after the induction of ischemia. Furthermore, it was possible to isolate the influence of laparotomy, as such, from the effect of ischemia. The free dissection of adhesions did not cause any significant shifts in the distribution of the test dose; and was of no im-

portance for the results. Only animals were used for analyses in which the formation of adhesions was insignificant, and on the same scale as in the laparotomized control material. The intestine of the fasting animal contracts strongly at death, and can be handled with comparatively less care, without any of its contents being displaced (Derblom, Johansson & Nylander, 1966).

It is only natural that, after an interval extending to 14 days, the established ischemia can have a relatively differentiated effect on both gastric emptying and propulsive motility in the small bowel. This explains the comparatively wide deviation in the results, with standard errors up to 10–20%. These differences in individual values, however, are due to biological, and not methodological, causes, and occur despite standardization of all the experimental conditions.

The primary effect of laparotomy was to practically deprive both the stomach and the intestine of their propulsive activity. With the lapse of time after the induction of ischemia there was gradual improvement in both gastric emptying and intestinal propulsion; and after 7 days the effect of laparotomy had almost entirely disappeared.

When intestinal ischemia was moderate (7 mesenteric arc) gastric emptying and propulsive activity of the intestine were initially accelerated (Nylander & Wikström, 1968). Only an assumption can be made to explain this apparently paradoxical phenomenon. Moderate ischemia might affect, through local irritation, a neuromuscular receptor mechanism, and release a long intestino-gastric reflex, which increases the propulsive activity in the gastrointestinal tract. Studies on reflex activity in the gastrointestinal tract have revealed a variety of reflexes. The peristaltic reflex is an intestino-intestinal reflex resulting in excitation above, and inhibition below, the stimulus. It is presumably local, and independent of central nervous connections. The intestino-intestinal reflex functions through autonomous innervation in the small bowel, and has an inhibitory effect, on the entire motility of the small bowel on distension of the organ. Less well-known is the intestino-gastric reflex, of which the afferent and efferent pathways are said to be vagal (Davenport, 1966; Daniel & Wiebe, 1966). It has an inhibitory effect on the stomach, on distention of the small bowel. Daniel & Wiebe studied gastroduodenal and duodeno-gastric reflexes, using simultaneous

recording of electrical and mechanical activity in the stomach and the duodenum. They found reciprocal, inhibitory, responses to distention between stomach and duodenum and suggested that the gastro-duodenal, inhibitory, reflex arc has an efferent limb which is adrenergic. Its afferent limb is unknown. The duodeno-gastric, inhibitory, reflex arc appears to have an afferent limb in the vagus and an adrenergic efferent limb which is sympathetic.

Thus, distention of the small bowel inhibits gastric emptying. The opposite condition, with accelerated emptying of the stomach is not known to exist. Theoretically such a reflex could however be conceived as occurring in connection with such local and "irritative" mural changes of a destructive or regenerative nature, as are a consequence of local ischemia. Moreover, such local contraction, which ischemia causes in the intestinal wall, can similarly elicit some receptor mechanism.

The tendency to *inhibition* of propulsive motility, which was observed after 24 hours in the group subjected to the lowest degree of ischemia, is possibly due to the ischemic section of the intestine being now the site of a more pronounced inflammatory reaction, which was verified histologically. The propulsive activity of the ischemic loop can then be assumed to be comparatively ineffective; and this reacts in some unknown way on the proximal section of the intestine and on the function of gastric emptying (intestino-intestinal inhibitory reflex?).

When, after 3-7 days, the inflammatory reaction had decreased, gastric emptying and intestinal propulsion again tended to become more effective than normally. This might be due to the local ischemic effect that now-again produced an intestino-gastric reflex, with accelerative influence.

After 14 days this effect had also disappeared.

When ischemia was more extensive (11 mes end arc), both gastric emptying and intestinal propulsion were, primarily, as greatly retarded as after laparotomy. Thus, the receptor mechanism for the hypothetical long intestinal reflex might not have been operative on account of the more pronounced ischemia (Nylander & Wikström, 1968). After 1-7 days, gastric emptying and intestinal propulsion were practically the same in both the ischemic groups; but after 14 days they

were retarded in the group subjected to the severest ischemia. It is most probable that the pronounced fibrosis, which was observed in the ischemic intestinal wall, interfered with both normal emptying of the stomach and propulsion in the small bowel.

As a result of the mathematical analysis of the propulsive gastrointestinal functions, in immediate connection with regional ischemia, Nylander & Wikström (1968) found that the stomach recovered its function more rapidly than did the small bowel. A corresponding analysis, made up to 14 days after the onset of ischemia, showed that already after 24 hours the gastrointestinal tract had recovered part of its propulsive capacity; and with the further lapse of time there was gradual normalization of the capacity of and relations between the two gastrointestinal motility functions, gastric emptying and propulsion in the small bowel.

The normal epithelium of the small bowel has a strong regenerative capacity. Leblond & Stevens (1948) found, when investigating ileal epithelium in white rats, that, especially in the crypts of Lieberkühn, a large number of cells were undergoing mitosis. The mean life of epithelial cells in the ileum was estimated at 1.4 days; and from this the conclusion was drawn that 71% of the ileal epithelium is renewed per day. The normal rate at which the intestinal mucous membrane is regenerated, is high, viz. up to 36 hours in both rat and man (Bertalanffy & Nagy, 1958; Leblond & Stevens, 1948; Leblond & Walker, 1956). Cameron & Khanna (1959) verified these findings, but studied also at the same time the histologic effect of general ischemia in the mucosa. The superior mesenteric artery was clamped for one hour. This resulted in complete necrosis of most of the villi. Rapid regeneration took place; and after 72 hours the histoarchitecture of the mucous membrane was regarded as entirely normal.

The regeneration of intestinal epithelium was reported on earlier by Florey & Harding (1935), who, after provoking artificial wounds in the duodenum of the cat, obtained complete healing with normal villous formation in 29 days. McMinn & Mitchell (1954) found that after excision of the mucosa and the submucosa in the cat's distal ileum, already after 24 hours a single layer of flat epithelium had grown out over the coagulum. Glotzer, Villegas, Anekamaya & Shaw (1962)

showed that even short ischemic periods damage the intestinal mucosa. When ischemia is less pronounced the injuries heal rapidly; whereas the healing of severely damaged mucous membrane may require several weeks.

Clinical experiences have shown that severe ischemic damage affecting the whole intestine can be healed (Shaw & Rutledge, 1957). Healing may also be associated with a long period of reduced function (Shaw & Maynard, 1958). Intestinal malabsorption, intermittent abdominal pains and loss of weight can, in such an aftercourse, be due to reduced flow of blood to the small bowel.

As cicatricial changes can occur after strangulated hernia (Garré, 1892; Ginzburg & Klein, 1928; Ginzburg & Oppenheimer, 1933; Barry, 1942; Raw, 1943; Hurwitt and co-workers, 1953), even restricted mesenteric vascular damage can cause changes in the intestinal wall, with the formation of strictures (Wangensteen, 1942; Rosenman & Gropper, 1955).

In previous investigations the ischemic period was accordingly short and immediately followed by reactive hyperemia with favourable conditions for healing of the tissues. Under the experimental conditions in this investigation, the ischemia probably remained comparatively unchanged throughout the observation period.

The histological observations show good agreement with the findings of earlier investigations. The good regenerative capacity of the intestinal epithelium was verified even when pronounced ischemia was present. After 7 days the epithelium had regenerated in the groups subjected to ischemia. It resulted in a fibrotic process in the intestinal wall, which, after 14 days, was most pronounced in the group with the severest ischemia.

Twenty-four hours after the induction of ischemia a rather pronounced inflammatory reaction appeared in the intestinal wall, with oedema and inflammatory cell infiltration. This might be a possible cause of the tendency, evident at this time, to retardation in the effectiveness of both gastric emptying and propulsion in the small bowel.

Similarly, the retardation of both these functions can probably be accounted for by the fibrosis gradually developed in the intestinal wall, and most pronounced in the group subjected to the severest ischemia.

Increased fibrosis was thus a more pronounced

local effect of the surgical ischemia and could, especially when the mucous membrane was destroyed, cause strictures which resulted in intestinal obstruction.

SUMMARY

The propulsive motility of the gastrointestinal tract was analyzed in the rat after regional ischemia in the small bowel had been allowed to persist for up to 14 days.

The material consisted of 702 animals.

Ischemia was produced by ligating a number of terminal vascular ramifications at the mesenteric attachment of the intestine and at a defined level. These were called mesenteric end arcades (mes end arc); and formed the connection between two adjoining secondary arches.

The regional ischemia was either moderate or pronounced, with ligation of 7 and 11 mes end arc, respectively.

The vasculo-anatomic method of evaluating the ischemia was correlated with the mucosal exchange circulation in the central part of the devascularized intestinal loop. The elimination of radio-iodide from the loop was used as an indirect parameter of its capillary flow, which in the defined mucosal area was considered to be the decisive variable when the iodide concentration of the test solution and the animal's iodide metabolism were kept constant.

In a series of *in vitro* experiments the transmural loss of iodide from the intestinal loop was analyzed when moderate intestinal ischemia had persisted for 7 and 14 days, respectively. Leakage from the loop was normal after 7 days, but considerably reduced after 14 days. This was correlated with histologically verified fibrosis which had developed in the intestinal wall.

Quantitative analyses were made of the propulsive motility of the gastrointestinal tract 1, 3, 7, and 14 days after the induction of ischemia.

Initially, the gastric emptying was greatly inhibited after laparotomy alone. Correspondingly, the propulsion in the small bowel was greatly retarded. This effect had almost completely disappeared after 7 days.

When moderate regional ischemia had been established both gastric emptying and propulsion in the small bowel were initially accelerated, but after 24 hours both functions were retarded. The

latter effect was correlated with an inflammatory reaction which appeared in the ischemic section of the intestine. It was suggested that this resulted in reduced propulsive effectiveness in the loop. Such local propulsive inability might react on proximal sections of the intestine and probably also on the stomach.

After 3-7 days, when the inflammatory reaction had decreased in intensity, the initial tendency to acceleration of both gastric emptying and intestinal propulsion was again observed.

The effect of the moderate ischemia had disappeared entirely after 14 days.

With more extensive ischemia both gastric emptying and propulsion in the small bowel were initially retarded to the same pronounced extent as after laparotomy alone. After 3-7 days the pro-

pulsive functions were accelerated to the same extent in both the ischemic groups; and after 14 days the functions were again retarded. Fibrosis was now pronounced in the ischemic section, and was assumed to interfere with normal propulsive functions.

Mathematical analysis with a special ratio method confirmed, essentially, these results and conclusions.

In the ischemic section of the small intestine histologic observations verified the occurrence of both an early inflammatory phase and a later one with fibrosis in the intestinal wall. When the local effect of the surgical ischemia was most pronounced, fibrosis had a proliferative character, with formation of strictures and intestinal obstruction.

References

- Barry, H. C. 1942. Fibrous stricture of the small intestine following strangulated hernia. *Brit J Surg* 30, 64-69.
- Berman, L. G. & Russo, F. R. 1950. Abdominal angina. *New Eng J Med* 242, 611-613.
- Bertalanffy, F. D. & Nagy, Katrina. 1958. The mitotic activity and renewal rate of human duodenal epithelium. *Anat Rec* 130, 271-272.
- Blalock, A. & Levy, S. E. 1939. Gradual complete occlusion of the celiac axis, the superior and inferior mesenteric arteries, with survival of animals: Effects of ischemia on blood pressure. *Surgery* 5, 175-178.
- Boley, S. J., Krieger, H., Schultz, L., Robinson, K., Siew, F. P., Allen, A. C. & Schwartz, S. 1965. Experimental aspects of peripheral vascular occlusion of the intestine. *Surg Gynec Obstet* 121, 789-794.
- Cameron, G. R. & Khanna, S. D. 1959. Regeneration of the intestinal villi after extensive mucosal infarction. *J Path and Bact* 77, 505-510.
- Councilman, W. T. 1894. Three cases of occlusion of the superior mesenteric artery. *Boston Med Surg J* 130, 410.
- Daniel, E. E. & Wiebe, G. E. 1966. Reciprocal inhibitory reflexes in stomach and duodenum. *Amer J Physiol* 211, 634-642.
- Davenport, H. W. 1966. *Physiology of the Digestive Tract*, 2nd ed, p. 67. Year Book Medical Publishers Inc., Chicago.
- Davis, B. B. 1921. Thrombosis and embolism of the mesenteric vessels. *Nebraska Med J* 6, 101-104.
- Derblom, H., Johansson, H. & Nylander, G. 1963. Thyroid hormone activity and gastrointestinal functions. An experimental study in the rat. *Acta Chir Scand*, Suppl. 307.
- 1966. A simple method of recording quantitatively certain gastrointestinal motility functions in the rat. *Acta Chir Scand* 132, 154-165.
- Dunphy, I. E. 1936. Abdominal pain of vascular origin. *Amer J Med Sci* 192, 109-113.
- Florey, H. V. & Harding, H. E. 1935. The healing of artificial defects of the duodenal mucosa. *J Path and Bact* 40, 211-218.
- Fock, G. 1962. Experimental studies of intestinal obstruction in rats. *Acta Chir Scand* Suppl. 292.
- Garcia, J. D. 1927. *Rev méd cubana* 38, 386.
- Garré, C. 1892. Ueber eine eigenartige Form von narbiger Darmstenose nach Brucheinklemmung. *Beitr klin Chir* 9, 187-197.
- Ginzburg, L. & Klein, E. 1928. Late intestinal stenosis following strangulated hernia. *Ann Surg* 88, 204-211.
- Ginzburg, L. & Oppenheimer, G. D. 1933. Non-specific granulomata of the intestines. *Ann Surg* 98, 1046-1062.
- Glutzer, D. J. & Shaw, R. S. 1959. Massive bowel infarction. *New Eng J Med* 260, 162-167.
- Glutzer, D. J., Villegas, A. H., Anekamaya, S. & Shaw, R. 1962. Healing of the intestine in experimental bowel infarction. *Ann Surg* 155, 183-190.
- Grevsten, S., Johansson, H. & Nylander, G. 1967. Analysis of a quantitative method of evaluation as applied to the propulsive gastrointestinal motility in the rat. *Acta Chir Scand* 133, 563-567.
- Griffith, J. & Farris, E. J. 1942. *The Rat in Laboratory Investigation*. J. B. Lippincott Company, Philadelphia.
- Grisell, T. L. 1949. Complications in treatment of incarcerated hernia with vasodilant drug. *J Indiana Med Ass* 42, 522-524.
- Hunt, J. N. 1959. Gastric emptying and secretion in man. *Physiol Rev* 39, 491-533.
- Hurwitt, E. S., Altman, S., Borow, M. & Rosenblatt, M. 1953. Intraabdominal arterial anastomoses. An experimental study. *Surgery* 34, 1043-1060.
- Johansson, H. 1966. Gastrointestinal motility function related to thyroid activity. *Acta Chir Scand*, Suppl. 359.
- Johansson, H. & Nylander, G. 1968. Analysis of the ileocecal passage in the rat. *Acta Chir Scand*. In press.
- Karcher, J. 1897. Ein Fall von Embolie der Art. Mes. *Sup. Corres-bl f Schweiz Aertze Basel* 18, 548.
- Klein, E. 1921. Embolism and thrombosis of the superior mesenteric artery. *Surg Gynec Obstet* 33, 385-405.
- Laufman, H. 1943. Gradual occlusion of the mesenteric vessels. *Surgery* 13, 406-410.
- 1950. Experimental evidence of factors concerned in the eventual recovery of strangulated intestine: Effects of massive penicillin therapy. *Surgery* 28, 509-515.
- Leblond, C. P. & Stevens, C. E. 1948. The constant renewal of the intestinal epithelium in the albino rat. *Anat Rec* 100, 357-371.
- Leblond, C. P. & Walker, B. E. 1956. Renewal of cell populations. *Phys Rev* 36, 255-276.
- Lillehei, R. C., Goott, B. & Miller, F. A. 1959. The physiological response of the small bowel of the dog to ischemia including prolonged *in vitro* preservation of the bowel with successful replacement and survival. *Ann Surg* 150, 543-559.
- McMinn, R. M. H. & Mitchell, J. E. 1954. The formation of villi following artificial lesions of the mucosa in the small intestine of the cat. *J Anat Lond* 88, 99-107.
- Medins, G. & Laufman, H. 1958. Hypothermia in mesenteric arterial and venous occlusion. *Ann Surg* 148, 747-754.
- Moore, T. 1941. Mesenteric vascular occlusion. *Brit J Surg* 28, 347-356.
- Nelson, L. E. & Kremen, A. J. 1950. Experimental occlusion of the superior mesenteric vessels with special reference to the rôle of intravascular thrombosis and its prevention by heparin. *Surg Gynec Obstet* 28, 819-826.

- Nylander, G. 1967. Gastric evacuation and propulsive intestinal motility following resection of the small intestine in the rat. *Acta Chir Scand* 133, 131-138.
- Nylander, G. & Svensson, A. 1968. Gastric emptying and propulsive intestinal motility in experimental intestinal obstruction. *Acta Chir Scand*. In press.
- Nylander, G. & Wikström, S. 1967. Gastric emptying and propulsive intestinal motility following partial gastric resections, gastroenteroanastomosis, and abdominal "trunk" vagotomy in the rat. *Acta Chir Scand* 133, 41-54.
- 1968. Propulsive gastrointestinal motility in regional and graded ischemia of the small bowel. An experimental study in the rat. I. Immediate results. *Acta Chir Scand*, Suppl. 385.
- Ortner, N. 1903. Zur Klinik der Angiosklerose der Darmarterien. (Dyspragia intermittens angiosclerotica intestinalis.) *Samml klin Vortr* 347 (Innere Med, No. 102), 855-904.
- Parkkulainen, K. V. 1962. Simple low small bowel obstruction. Experimental study on rabbits, guinea pigs and rats. *Acta Chir Scand*, Suppl. 290.
- Raw, S. C. 1943. Stricture of small bowel following strangulated hernia. *Lancet* 244, 460.
- Reed, L. B. 1921. *Ann Surg* 74, 797. Cit. by T. Moore.
- Reich, A. 1913. Embolie und Thrombose der Mesenterialgefäße. *Ergebn Chir Orthop* 7, 515-597.
- Rosenman, L. D. & Gropper, A. N. 1955. Small intestine stenosis caused by infarction: An unusual sequel of mesenteric artery embolism. *Ann Surg* 141, 254-262.
- Shaw, R. S. & Rutledge, R. H. 1957. Superior mesenteric artery embolectomy in the treatment of massive mesenteric infarction. *New Eng J Med* 257, 595-598.
- Shaw, R. S. & Maynard, E. P. 1958. Acute and chronic thrombosis of the mesenteric arteries associated with malabsorption. Report of two cases successfully treated by thromboendarterectomy. *New Eng J Med* 258, 874-878.
- Shay, H., Komarov, S. A., Fels, S. S., Meranze, D., Gruenstein, M. & Siplet, H. 1945. A simple method for the uniform production of gastric ulceration in the rat. *Gastroenterology* 5, 43-61.
- Virchow, R. 1854. Verstopfung der Gekrösarterie durch einen eingewanderten Propf. *Verh phys-med Ges Würzb* 40, 341-349.
- Wangenstein, O. H. 1942. *Intestinal Obstruction: A Physiological and Clinical Consideration with Emphasis on Therapy, Including Description of Operative Procedures*, 2nd ed., p. 292. Springfield, Ill. Charles C. Thomas, Publisher.
- Weyrauch, Helen, B. & De Garis, C. F. 1937. Normal and interrupted vascular patterns in the intestinal mesentery of the rat. An experimental study on collateral circulation. *Amer J Anat* 61, 343-372.

